"FLUID ADMINISTRATION IN NEONATES WITH HYPERBILIRUBINEMIA - RANDOMISED CONTROLLED TRIAL"

By

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Dissertation

Submitted to the
KLE Academy of Higher Education and Research
Belagavi, Karnataka
In partial fulfilment of the requirements for the degree of

M. D. (Doctor of Medicine)

IN

PAEDIATRICS

Under the Guidance of

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ACKNOWLEDGEMENT

I would like to humbly extend my gratitude to all the people who have supported and guided me during this period.

I would like to start by expressing my sincere thanks to my guide, ***Dr. MANISHA BHANDANKAR*** ***M.D. MRCPCH, PhD*** *Professor, Department of Paediatrics, Jawaharlal Nehru Medical College, Belagavi, for her continuous supervision, able guidance and unparalleled encouragement provided to me through out the course of the study. Without her immense professional insight and support it would not have been possible for me to complete this dissertation. She has played a pivotal role in shaping my outlook towards practice, and teaching. Also would like to thank her for always being patient with me.*

It gives me great pleasure to express my gratitude and sincere thanks to ***Dr. M.V Patil*** ***MD*** *Professor and Head, Department of Paediatrics, Jawaharlal Nehru Medical College for his guidance, encouragement and support during my postgraduate course.*

I am extremely grateful to ***Dr. N. S Mahantshetti,*** ***MD,*** *Principal and Professor, Department of Paediatrics, Jawaharlal Nehru Medical College, for her constant support and encouragement. She is the driving force to keep me strong even during the difficult times. I would like to thank her for making me realise my capabilities.*

I would also like to thank ***Dr. V. D. Patil*** ***MD, DCH*** *Professor, Department of Paediatrics, KAHER, Belagavi. His encouragement and support have been a great source of inspiration and a driving force in this extensive training program.*

I am extremely grateful to ***Dr Roopa M Bellad*** ***M.D*** *Professor, Dept of Pediatrics, Jawaharlal Nehru Medical College, for providing her constant support.*

I am also extremely thankful to ***Dr. S. M. Dhaded*** ***MD DM,*** ***Dr. Sujatha M Jali*** ***MD,*** ***Dr. R. M Wali, Dr. Mahesh Kamate*** ***MD, DM,*** ***Dr. Veeresh Manvi*** ***MD,*** ***Dr. Tanmaya Metgud*** ***MD,*** ***Dr Dnyanesh Kamble*** ***MD,*** ***Dr Abhilasha S, Dr Santosh Kurbet, Dr Supriya Patil, Dr Meenakshi BR, Dr. Bhavana Koppad*** ***MD,*** ***Dr. Sonali Bijjargi*** ***MD*** *,* ***Dr. Zeeshan Desai*** ***MD*** *for their valuable suggestions and encouragement.*

I owe an immense debt of gratitude to my beloved family. To my mother ***Mrs. Neelam Anand, Father Mr. Shakti Anand., Chachi ji Mrs Kamal Anand and Chacha ji Mr Sanjeev Anand*** *for their constant support.*

To my Brothers and Bhabis Adv. Kapil Anand, Mrs Sonia Anand, Dr. Deep Anand, Dr Neha Anand ,Adv. Harshit Anand and Sister Adv. Divya Anand *for always pushing me to do better.*

To little blossoms ***Aishani, Vaanya, Inayat and Adhiraj*** *for always giving me positivity*

I would also like to thank ***Dr Daisy Ahluwalia*** *for her constant support throughout.*

To my friends Pramod, Rohan, Mubarish, Nishant, Ayush, Sudeep, Gopika, Neha, Anushree, Srinivas and Nishant for being my greatest support and a family away from home. To my juniors for always pushing me to do better.

I extend my sincere thanks to Nursing staff from NICU for their cooperation and helping me complete my study.

I would like to acknowledge the tireless work of ***Mr. Arun&Mr. Anand*** *of Shri Vighneshwara Associates Computers of J.N.M.C for excellent data processing and completion of this dissertation*

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LIST OF ABBREVIATIONS USED

TSB	-	Total Serum Bilirubin
TB	-	Total Bilirubin
DB	-	Direct Bilirubin
NICU	-	Neonatal Intensive Care Unit
POG	-	Period of Gestation
IV	-	Intra venous
ORS	-	Oral Rehydration Solution
WHO	-	World Health Organisation
BIE	-	Bilirubin Induced Encephalopathy
IMR	-	Infant Mortality Rate
DBF	-	Direct Breast Feeding
EBF	-	Exclusive breastfeeding
NON EBF	-	Non Exclusive Breastfeeding
LSCS	-	Lower segment caesarean section
NVD	-	Normal vaginal Delivery
NNPD	-	National Neonatal-Perinatal Database
AAP	-	American Academy of Pediatrics
BET	-	Blood Exchange Transfusion
DVET	-	Double Volume Blood Exchange Transfusion
HPLC	-	High Performance Liquid Chromatography
ETCO	-	End tidal Carbon Monoxide
IVIG	-	Intravenous Immunoglobulin
STB	-	Serum Total Bilirubin

ABSTRACT

Background : Hyperbilirubinemia is a common neonatal problem occurring in 60% term and 80% preterm neonates. This is due to increased breakdown of red blood cells and decreased clearance of bilirubin, which in turn is due to immaturity of the conjugation process in the liver and increased enterohepatic circulation. There is an indirect evidence of subclinical dehydration in large proportion of neonates with “idiopathic” hyperbilirubinemia. Majority of neonates are exclusively breast fed and due to increased sodium content especially in primiparous mothers and poor sucking by a low birth weight baby can cause dehydration. Various studies have shown that fluid supplementation can decrease total serum bilirubin levels more rapidly and decreases the need for exchange transfusion. Extra fluid administration can decrease enterohepatic circulation, dilute the serum bilirubin and increase renal excretion of water soluble photo isomers in urine. Further inadequate oral feeding in sleepy neonates due to significant hyperbilirubinemia along with insensible water loss during phototherapy can predispose to worsening of hyperbilirubinemia in new borns not receiving extra fluids

Objective

To evaluate the efficacy of oral fluid (ORS in double dilution) supplementation in accelerating the decline of serum bilirubin with intensive phototherapy among healthy term and late preterm neonates with hyperbilirubinemia.

Study Design :

A one year Hospital Based Randomised Controlled Trail was conducted from June 2020 to May 2021 in KLE’S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Methods :

The Present study was conducted among the neonates admitted in NICU for Hyperbilirubinemia Treatment at KLE's Dr Prabhakar Kore Hospital Attached to J N Medical College , Belagavi. The Neonates born in the hospital at 34weeks+1day or more weeks of gestation and admitted with hyperbilirubinemia (any baby coming in phototherapyrange) was included in the study

Neonates who required the need of intensive care for other morbidities, major congenital malformation, STB (Serum Total Bilirubin) at admission higher than threshold for exchange transfusion, clinical signs of dehydration needing administration of intravenous fluid were excluded from the study .

The research covered neonates in a hospital at 34 weeks+1 day or more of gestation and hospitalised with hyperbilirubinemia (any infant in the phototherapy range). Enrolled newborns were randomly assigned to one of two research groups: oral fluid supplementation (oral rehydration solution) or the control group in a 1:1 ratio. One of the two groups got 50ml/kg of additional fluids (ORS double dilution) and standard therapy. Over the course of 16 hours, ORS was delivered in 8 split feeds. A total of 33 study subjects were enrolled in each group for the purpose of the study and followed up till the end point of the study.

Results:

In the present study 48.5% of the newborns were male and 51.5% were female in the study group. In the Control Group 45.5% were male and 54.5/5 were female . The mean Birth weight of in the study group was 2921.82$\pm$437.0 gms and in the control group it was 2706.36$\pm$ 407.19 gms (p value 0.042). The Mean age at the time of admission to NICU for the purpose of treatment was found to be 82.36$\pm$ 29.3 hours in the case group and 86.52 $\pm$35.78 hours in control group .At the time of admission the mean total serum bilirubin was 17.18$\pm$3.20 mg/dl in study group and 15.91$\pm$2.70 in control group. 24 hours post admission the mean total serum bilirubin level was

11.91±3.61 mg/dl in study group and 12.27±2.58 mg/dl , 48 hours the mean total serum bilirubin was 9.76± 2.49 mg/dl in study group and 9.73±2.23 mg/dl in control group. The mean rate of fall in TSB was 5.37mg/dl in 24 hours among the study group while it was 3.61mg/dl in 24hrs in the control group. This difference was statistically significant (p value 0.001).Further, the rate of fall in TSB between 24hrs and 48hrs of admission among study group was 1.99mg/dl and in control group it was 2.53mg/dl (p value 0.286).There was no statistically difference in fall of TSB after 48hrs in both the groups.

Conclusion:

The role of oral ORS to provide extra fluid for healthy neonates with neonatal hyperbilirubinemia in addition to exclusive breast feeding showed that it augments the rate of fall of TSB in the first 48hrs. ORS supplementation was found to be safe and easily implementable. This intervention could be useful in the Level 2 NICUs in the periphery to decrease the duration of NICU stay and prevention of infections secondary to IV fluids.

Keywords: Newborn, Premature, Hyperbilirubumenia, Fluids, Phototherapy, Ors

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INTRODUCTION :

Hyperbilirubinemia is the most prevalent condition among neonates, with a prevalence of 70 to 80 percent. Bilirubin is released when RBCs are broken down, and it is deposited in the skin and mucus membrane of infants. When compared to term neonates, it is considered to be more prevalent with preterm babies. In the majority of instances, it manifests in a moderate to temporary form. In 5 to 10% of neonates that need intervention, a clinically identifiable type of Hyperbilirubinemia is present.[1,2,3]

In India, the incidence of newborn hyperbilirubinemia was found to be 3.3 percent in home live births and 22.1 percent morbidity among extramural admissions in the National Neonatal Perinatal Database.[4]

In a high number of infants with "idiopathic" hyperbilirubinemia, there is indirect evidence of subclinical dehydration. The majority of newborns are exclusively breastfed, and dehydration may occur as a result of high salt content, particularly in primiparous moms, With a low-birth-weight newborn sucking poorly is also seen.[5,6,7]

Bilirubin Metabolism : [8]

The bulk of bilirubin is created by the metabolism of haemoglobin, which is introduced to the circulatory system by naturally decommissioned or pathologically damaged erythrocytes during two stages of Haem catabolism in the reticuloendothelial system.It is mostly caused by red cell disintegration in infants, with a quarter of the cases being caused by inadequate erythropoiesis.

In most cases, the quantity of free bilirubin circulating in a jaundiced neonate is rather little. It is transported reversibly through the circulation by binding to serum albumin in the ratio of 3:1.The quantity of bilirubin circulated in the newborn is quite minimal under typical circumstances.

Complications: [9]

Bilurubin Induced Encephalopathy is a syndrome that develops when Indirect Hyperbilirubinemia is not diagnosed and treated promptly, resulting in neurological abnormalities in the baby. When compared to industrialised nations, this syndrome is more common among babies in impoverished countries. All newborns with risk factors for elevated indirect bilurubin levels in their blood are known to be at risk for BIE, which is more frequent among newborns.

The Normal Pattern of Neonatal Jaundice: [10]

Unconjugated bilurbin is excreted by the foetus via the placenta and mother's liver .The Bilurubin level at delivery was reported to be 1-2 mg/dl in those without Fetal hyperbilirubinemia or maternal liver illness. Jaundice is characterised as normal or pathological depending on the amount and source of bilirubin.

Physiological Hyperbilirubinemia :[10]

It develops as a result of the liver's physiological immaturity in dealing with the increased generation of bilurubin in neonates. Jaundice occurs between 24 and 72 hours after delivery. By the third day after delivery, Total Serum Bilurubin generally reaches a high of 6 to 8 mg/dl and then starts to decline gradually. A result of up to 12mg/dl is regarded to be within the physiological normal range. By the fifth day of life, the peak

in preterm newborns may reach 10 to 12 mg/dl, and it can rise over 15 mg/dl even in individuals who have no special abnormalities in bilirubin metabolism.[10,11]

Pathological Hyperbilirubinemia : [11]

Pathological hyperbilirubinemia arises when total blood Bilurubin concentrations in newborns surpass fifteen mg/dl within 24 hoours ,and the value is still at 10 mg/dl after 48 hours , and between Twelve to thirteen mg/dl on the third day..

When the value of Total serum bilirubin increases > 17 mg/dl should be considered pathogenic, requiring further investigation and intervention to discover the cause.

The term "pathological jaundice" refers to jaundice that appears within 24 hours after birth and has a peak total serum level. Clinical jaundice that lasts longer than two weeks in term neonates and three weeks in preterm newborns., as well as a bilirubin level that is greater than the usual range. Increased conjugated bilirubin levels, black pee stains on clothes, and light-colored faeces are all signs of pathological jaundice...[12,13,14]

Two of the most frequent treatment choices for hyperbilirubinemia patients .

1. Phototherapy and

2. Double volume blood exchange transfusion.

The idea of phototherapy is to convert insoluble uconjugated bilurbin to water soluble compounds that may be eliminated via urine and faeces. By eliminating 80-85 percent of the circulating RBCs and decreasing the bilirubin load, a double volume exchange transfusion may help.[12,13]

Fluid supplementation has been shown in past trials to aid in the quick reduction of total blood bilirubin levels, hence lowering the requirement for exchange transfusion. The enterohepatic circulation is inhibited, serum bilirubin is further diluted, and gets eliminated by renal excretion of the photo isomers which is water soluble in the urine is promoted by supplementing with more fluid.

Extra intravenous fluid supplementation/oral ORS has been shown in several trials to decrease phototherapy hours and exchange transfusion rates. Because hyperbilirubinemia is the most prevalent morbidity in newborns, prompt treatment is critical. As a result, we are doing this research to see how effective oral fluid supplementation is in infants with hyperbilirubinemia.

Phototherapy is the most common treatment for newborn hyperbilirubinemia. Fluid supplementation, in addition to phototherapy, may assist to reduce the risk of increasing blood bilirubin levels.

The majority of studies have been conducted in term neonates using IV fluids, which may be difficult in peripheral settings due to complications such as hospital-acquired infections and thrombophlebitis, so there is a need to examine the effect of oral fluid supplementation in both late preterm and term neonates..[14,15,16]

Presently babies who need extra fluid are being supplemented with formula feeds which undermines the confidence of mother in exclusive breast feeding.

OBJECTIVES :

Primary objective-

To see whether oral fluid (ORS in twofold dilution) supplementation may help accelerate the decrease of serum bilirubin in healthy term and late preterm newborns with hyperbilirubinemia who were receiving extensive phototherapy.

Secondary objective-

1.) To monitor changes in weight loss pattern in both the groups.

2.) To assess the acceptance of giving ORS solution over formula milk among the mothers

REVIEW OF LITERATURE:

Bilirubin has been studied for hundreds of years, and infants with jaundice have been identified. Modern evaluations of jaundice in neonates seem to have started around the end of the eighteenth century. Jean Baptiste Thimotee Baumes performed one of the pieces (1806).[17]

He describes how infant jaundice may have been connected to or induced by lethargy, low intake, signs and symptoms of cerebral association, and a delay in meconium passage. In 1853, Condie discovered that jaundice in a newborn child was linked to a lack of meconium discharge.[18]

Johannes Orth noted the colouring of the nerve system in a kernicteric newborn in 1875, as well as the existence of yellowish and reddish tincture susbstnaces in neonate appendages..[18]

He noticed that neurons in the basal ganglia were stained yellowish, but neurons in other areas of the body were not. With the Assist microscope, he examined the Nervous System (Brain) and noticed that neurons in the basal ganglia were stained yellowish, but those in neighbouring areas were not.

In 1904, Chirstian Schmorl coined the name "Kernicterus," and he also noted that if the brain specimen is not stored in Formalin, the yellowish stain eventually fades.[19]

In the year 1908, Rolleston H D and Arkwright J an et al discovered icterus gravis neonatorum among households of the same family, as well as instances of separate families with jaundice and kernicterus..[20]

In 1914, Gutherie L published the first report on Kernicterus, as well as the link between brain injury and hyperbilirubinemia among the newborns with erythroblastosis fetalis .[21]

Diamond et colleagues revealed the pathogenesis of erythroblastosis fetalis for the first time in 1932..[22]

Another severe form of jaundice has been observed, in which newborn jaundice is linked to icterus gravis and causes severe anaemia, as well as unusual neurological signs and mortality. When the blood grouping among people was researched in depth after many years, it was shown to be caused by an alloimmune hemolytic disease.

In 1904, the involvement of Rh Antigen in red blood cells in the development of the illness in certain families was established.

In 1944, Blackfan et al published a book on blood disorders in infants, which included a detailed description of the genesis of hemolytic illness as well as the procedure of exchange transfusion among newborns to treat the problem.[23]

When necessary, John Barrett et colleagues found many techniques of exchange transfusion..[24]

Vaughan, et al., linked erythroblastosis with kernicterus in 1946.[25]

In 1963, Schenker et al discovered that unconjugated bilirubin can readily cross the placenta, proving that foetal hyperbilirubinemia was not present throughout intrauterine life and that its level started to rise in the foetus shortly after delivery. [26] The discovery of Rh immune anti globulin in 1968 was linked to a reduction in birth rates in the 1970s.[27]

Ehrenreich discovered the existence of the blue pigment in urine in 1883 when he mixed Diazo reagent with bilirubin.

Van Den Bergh developed the diazo reaction in 1918..[28]

In 1956, Schmid et al. discovered that bilirubin glucuronide was the direct moiety.. [29]

In 1959, Odell looked into the bilirubin-protein binding. [30]

A accidental encounter at the Rochford Hospital in Essex, England, in 1956 led to the most important discovery of the use of phototherapy. Fresh air and sunshine from within the garden, according to the sister in charge of the preterm infant section's ward (In charge Nurse), were good to the toddlers. After Dr. Cremer's research was published in the Lancet in 1958, paediatricians all across the United Kingdom began to employ phototherapy as a therapeutic method.[31]

In addition, in the year 1968, Lucey et al. produced another important document. Dr. Lucey, who dubbed himself the "Prince of Light" with much humour, was the most honest proponent of phototherapy.[32]

The hypothesis of rapid elimination of products following phototherapy via bile and urine was proposed by Ostrow J et al..[33]

Heme metabolism is stated to produce bilirubin as an end result. Heme is found in haemoglobin as well as a variety of oxidative enzymes, including Mitochondrial cytochromes and Microsome P 450 cytochromes in the liver. Roughly 85 percent of bilirubin in plasma is erythropoietic, whereas nearly 15 percent is non-erythropoietic. It obtains its erythropoietic fractions from normal ageing erythrocytes in the blood as well as the juvenile faculty red cells found in bone marrow. .[34,35]

The production of bilirubin by reticulo-endothelium in every organ, notably the spleen, liver, and bone marrow, is consistent with the importance of monocytic macrophages. Bilirubin is made by hepatocytes from non-erythropoietic heme. Heme's tetrapyrrolic ring is broken by an oxygenase. The tetrapyrrolic molecule is used to build a tetrapyrrolic collection without iron..[36]

In the 1960s, heme oxygenase was identified to be a critical enzyme in the manufacture of bilirubin. Heme is converted to biliverdin, a light-colored pigment, in haemoglobin and heme-containing proteins. Biliverdin reductase is an enzyme that transforms biliverdin to unconjugated bilirubin, a pigment that is orange-yellow in colour.[37]

Bilirubin Biochemistry:[38,39]

The reticuloendothelial system produces bilirubin as a waste product of heme catabolism at a low level. Heme is an oxygen-transporting component of haemoglobin. The release of heme from haemoglobin is caused by the destruction of purple blood cells. The initial stage in the charge-proscribing process is performed by the enzyme heme oxygenase-1, which converts heme to biliverdinIXa. As a result, equimolar quantities of free iron and carbon monoxide are created. Carbon monoxide is expelled via the lungs, while iron is used to make haemoglobin. Biliverdin is a blue-green heme chemical that is water soluble and non-toxic. Biliverdin is easily eliminated by the liver and kidneys. Biliverdin reductase transforms biliverdin to bilirubin IXa in animals. The most poisonous isomer of bilirubin is bilirubin IXa. Because bilirubin is water insoluble at physiological pH, it can pass through all organic membranes, including the blood-brain barrier. When 1 gramme of haemoglobin is broken down, 34 mg of bilirubin is

produced. Before being expelled as bile, bilirubin must be conjugated by the liver enzyme uridinediphosphoglucuronateglucuronosyltransferase. A -level haem catabolism produces bilirubin in the reticuloendothelial system.

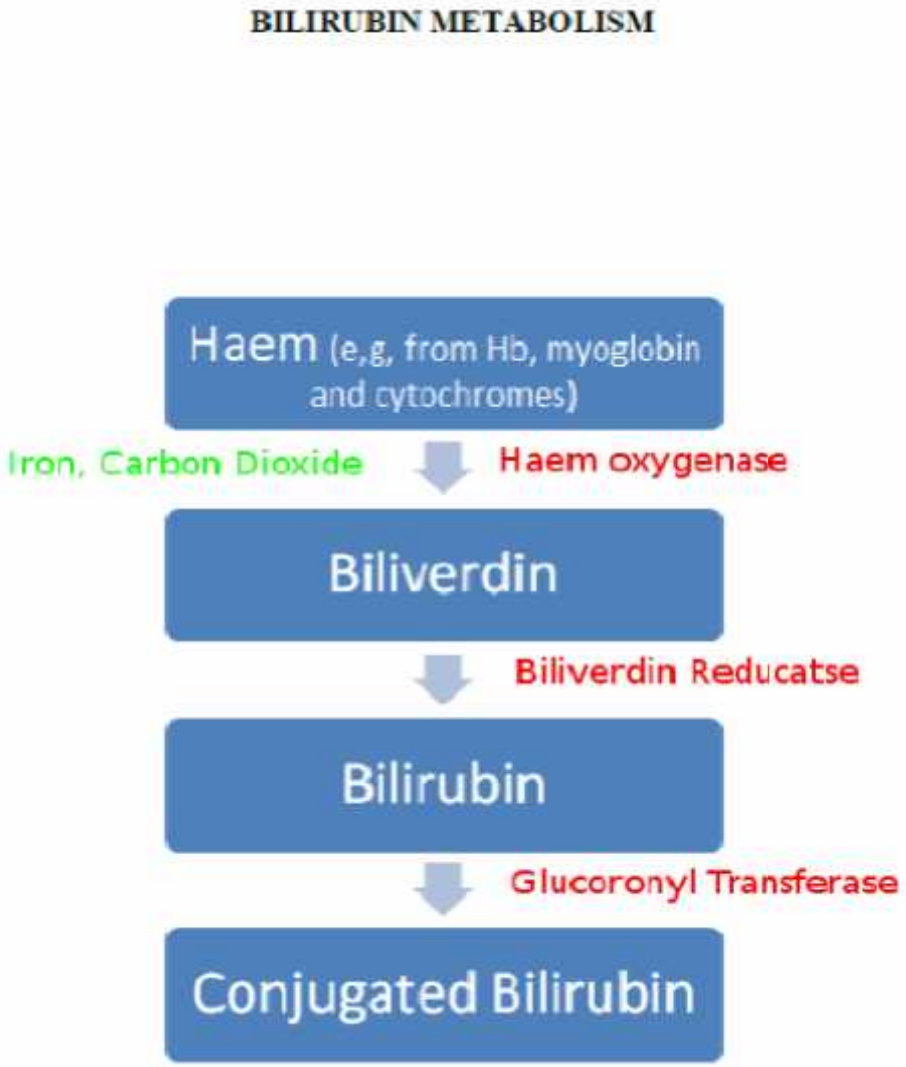
The breakdown of red blood cells in infants produces the majority of bilirubin, Up to a fifth of it comes from faulty erythropoiesis and other haem-containing compounds like cytochromes and myoglobin .

With a molar bilirubin to albumin ratio of up to 3:1, bilirubin is delivered bound reversibly to serum albumin on high and low affinity sites throughout the circulation. In a jaundiced newborn, the quantity of free bilirubin circulating is minimal under normal circumstances.

Bilirubin is conjugated with glucuronic acid in the endoplasmic reticulum of the liver to form water-soluble mono and diglucuronides of bilirubin. Uridine diphosphoglucuronosyl transferase, a microsomal liver enzyme, catalyses these reactions (UDPGT). Conjugated bilirubin is actively transported out of the liver cell and into the biliary canaliculi as a component of bile in monoglucuronide and diglucuronide forms.

In humans, the bulk of conjugated bilirubin is converted to urobilinogen by colonic flora before being eliminated in the faeces as stercobilinogen. In the neonate, a considerable quantity is degraded by -glucuronidase within the small intestine, resulting in unconjugated bilirubin, which may then be re-injected into the circulating pool

through the enterohepatic circulation..



Bilirubin Transport[40]

At pH 7.4, unconjugated bilirubin is insoluble in water. Albumin binds significantly more easily in plasma than it does in blood. Unconjugated bilirubin binds to albumin at a rate of around 7 to 8 mg/dl per gramme of albumin. Plasma binding potential is lower in newborns than in adults. Reduced binding might be related to a lack of awareness of serum albumin or a reduction in binding capacity. Unbound bilirubin is thought to be a more sensitive predictor of bilirubin-induced neurological impairment. However, there may currently be no reliable method for grading the unbound bilirubin portion.

In circulation, bilirubin comes in four distinct forms.

• unconjugated bilirubin that is reversibly bound to albumin, • unconjugated bilirubin that is not linked to albumin, • conjugated bilirubin that is released from the liver and expelled by the renal or biliary system, and • conjugated bilirubin that is covalently bonded to albumin.

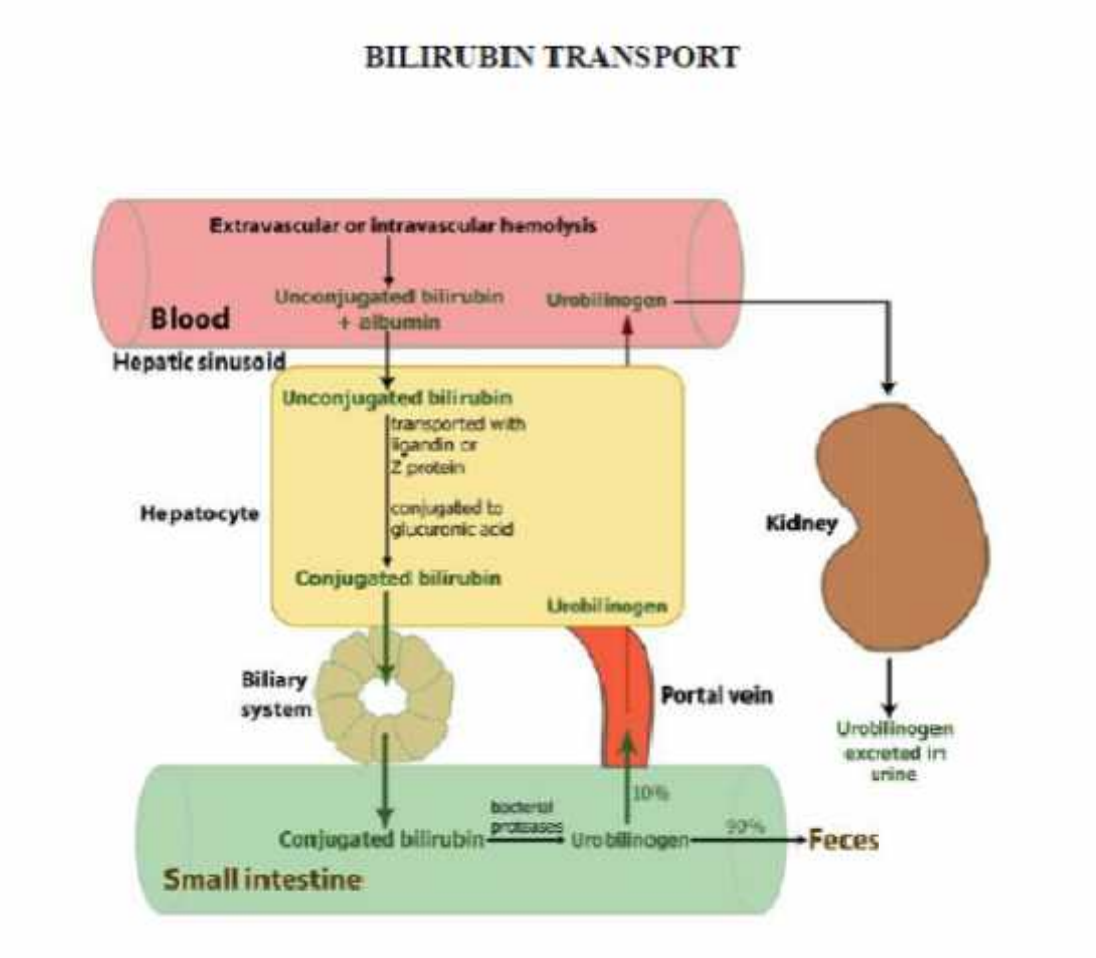
Unconjugated bilirubin levels rise in newborns owing to increased hemolysis or decreased bilirubin glucuronidation. The conjugated bilirubin levels rise in the presence of Cholestatic situations. In new borns with liver problems, bilirubin levels will rise, especially in those with long-term conjugated hyperbilirubinemia.

Hepatic Uptake [41,42]

Before entering the hepatocytes, bilirubin separates from simple protein. The liver absorbs bilirubin pigment in part by carrier-mediated diffusion and in part through organic ion transporter proteins. Unconjugated bilirubin is linked to ligandin inside the hepatocyte. Ligandins are the most important intracellular transport proteins because they bind to bilirubin and keep the dangerous unbound portion of bilirubin low. Z protein, a hepatocyte carrier protein, has a decreased affinity for bilirubin. The total serum bilirubin concentration at any given moment is determined by the balance between the rate of bilirubin discharge into the circulation and its removal.

Reduced hepatic absorption of unconjugated hyperbilirubin is the primary cause of physiological jaundice. Thus, in the development of unconjugated hyperbilirubinemia during the first three to four days of life, diminished bilirubin absorption is not regarded

to be as critical as immature bilirubin conjugation. When conjugated bilirubin reaches adult levels in the second week of life, the reduced absorption of bilirubin by the liver contributes to hyperbilirubinemia.



Bilirubin Conjugation [40,41,42]

Unconjugated bilirubin should be made water soluble for bile excretion. This two-step method of turning water insoluble bilirubin to water soluble bilirubin involves conjugating it with glucuronic acid..

It is carried to the smooth endoplasmic reticulum in the liver, where the enzyme uridine diphosphateglucuronosyl transferase performs the conjugation step (UDPGT-1). Bilirubin catalyses the transfer of one glucuronic acid molecule to generate the bilirubin monoglucuronide with the aid of this enzyme. Unconjugated hyperbilirubinemia is caused when the enzyme's capability is less than one percent.

The bilirubin monoglucuronide becomes a water soluble molecule after conjugation with the enzyme, and it is expelled in bile, where it is changed from monoglucuronide to diglucuronide. The process of conjugation of the second glucuronide molecule to monoglucuronide, which is mediated by the enzyme UGT1A1 in the endoplasmic reticulum, is the next step. UDP glucuronide glucuronosyl transferase is particularly important in the second phase of conversion.

The bilirubin generated as a result is a water soluble component that may be readily eliminated via the gastrointestinal system. The conjugated bilirubin's enhanced water soluble component will reduce the amount of bilirubin that is reabsorbed from the colon. In adults, this glucuronide conjugation contributes to about 90% of total bilirubin disposal. The remaining bilirubin is rendered water soluble by conjugation with substances like as glucose, xylose, and sulphates, accounting for about 10% of the total bilirubin expelled by the bile.

The majority of research found that infants have a deficit of this enzyme, which results in greater bilirubin levels in the first few days of life. By the end of the fourth day, the

newborn's liver capacity had reached that of an adult, with 75 percent of all bilirubin conjugation taking place.

The most prevalent kind of conjugated bilirubin in neonates is bilirubin monoglucuronides. In term babies, UGT activity is around 1% of what it is in adults. Premature newborns have significantly lower levels. UGT activity increases steadily until it reaches adult levels at 3 months of life.

Excretion Of Bilirubin [39,40,41]

Water Soluble Conjugated bilirubin excretion is an energy-dependent process. Along with bile acids, phospholipids, and cholesterol, conjugated bilirubin is integrated into mixed micelles. After then, the bilirubin is expelled in a concentration gradient. Bile bilirubin content is around 100 times that of hepatocyte cytoplasm. A high bilirubin pool in newborn neonates must be removed in circumstances such as hemolytic illness of the newborn. The efflux of conjugated bilirubin into the serum occurs when the bilirubin burden exceeds the excretory capacity.

Hepatic excretory step is significantly inhibited in the presence of hepatocyte damage and biliary blockage, resulting in efflux of conjugated bilirubin into the blood. Conjugated hyperbilirubinemia is the outcome of this.

Enterohepatic Absorption Of Bilirubin[41]

Bilirubin that has been conjugated cannot be absorbed via the colon. Bilirubin mono- and diglucuronides, on the other hand, are very unstable and easily hydrolyzed to unconjugated bilirubin. Unconjugated bilirubin may now easily pass through the intestinal mucosa. The enterohepatic circulation of bilirubin is what it's called.

This adds to the pool of circulating unconjugated bilirubin, which is then given to the liver for conjugation. The enteric mucosal enzyme -glucuronidase is found at high amounts in both term and preterm infants. According to studies, around 25% of bilirubin discharged into the intestines is reabsorbed after being converted to unconjugated bilirubin. Bilirubin excreted in the bile is unaltered and excreted in the faeces in 10% of cases.

The bilirubin that remains is transformed to urobilinoids and eliminated in the stool. When compared to adults, newborns have a higher level of unconjugated bilirubin in their intestines, resulting in greater enterohepatic circulation. Increased bilirubin production and meconium bilirubin concentration have resulted in an excess of unconjugated bilirubin. Furthermore, since newborns lack the intestinal bacterial flora necessary to convert bilirubin to urobilinogen, the amount of bilirubin accessible in the gut is increased, resulting in more bilirubin being absorbed. The activity of glucuronidase in intestinal mucosal cells is also elevated in newborns, resulting in enhanced hydrolysis of conjugated bilirubin.

Neonatal Hyperbilirubinemia [43,44,45]

Newborn icterus or jaundice, otherwise known as hyperbilirubinemia in the neonatal period as icteric, is a yellowish staining of a neonate's mucous membrane caused by high blood bilirubin levels.

Neonatal hyperbilirubinemia is caused by variations in bilirubin synthesis, metabolism, and excretion as a result of developmental changes. It's characterised by an increase in bilirubin burden on immature hepatocytes and a reduction in bilirubin elimination in the liver. The increased hepatic bilirubin burden is caused by bilirubin overproduction,

which is caused by a greater red cell mass, a shorter red cell life span, and, in certain babies, hemolytic circumstances that speed up red cell turnover.

Hepatic bilirubin absorption and conjugation are decreased in infants, resulting in lower bilirubin clearance. Furthermore, increased bilirubin reabsorption from the intestines, as well as increased enterohepatic circulation, lowers bilirubin excretion and raises bilirubin burden on the immature liver.

Bilirubin has a tendency to lodge in the skin and mucous membranes of neonates, resulting in a yellowish colouring. It may also accumulate in the brain, causing bilirubin encephalopathy, both acute and chronic. To comprehend the treatment principles and possible consequences, a full understanding of the bilirubin metabolism is required.

In newborns, a natural rise in serum bilirubin occurs, which is not to be confused with hyperbilirubinemia. Physiologic bilirubinemia is the proper word. The bilirubin level reaches its highest point around day 5 of life.

The breakdown of RBCs generated earlier in pregnancy resulted in a 150 percent rise in bilirubin production per unit of body weight during the later weeks of pregnancy. Before 30 weeks of pregnancy, the UGT activity of a human foetus is exceedingly low, about 0.1 percent of adult activity. UGT activity steadily rises until it reaches roughly 1% at the end of the period. The physiologic bilirubinemia in newborns is caused by decreased UGT activity, increased bilirubin synthesis, increased enterohepatic

circulation, and reduced hepatic absorption. Hyperbilirubinemia will not arise in the foetus since the unconjugated bilirubin generated will be removed by the placenta.

Even with severe hemolytic conditions such as isoimmunization, jaundice is generally modest, with anaemia being the most noticeable symptom. When the infant is detached from the placenta after delivery, bilirubin levels rise. In the case of hemolytic disorders, the rise in serum bilirubin is considerable. Because the placenta is impermeable to conjugated bilirubin, conjugated bilirubinemia should be considered if jaundice occurs immediately after delivery.

Conjugation happens in the liver of the foetus and is discharged into the intestines. Glucuronidase activity is detected in meconium, and it is responsible for converting conjugated bilirubin to unconjugated bilirubin, which is then reabsorbed into the circulation. The procedure may guard against severe hyperbilirubinemia caused by intrauterine hemolysis.

The bilirubin content in the amniotic fluid rises in severe hemolytic illness of the foetus. After direct transfer from the placenta or cord blood arteries, bilirubin levels may rise. The bilirubin levels in amniotic fluid is used as a marker for foetal anaemia.

Total bilirubin levels rise steadily in term newborns, reaching a peak concentration between 72 and 120 hours. The duration of the peak bilirubin concentration differed significantly by race. The peak of the white population is frequently sooner than the peak of the Asian population. Nursing prevalence has a considerable impact on peak bilirubin concentration, with breastfeeding infants having a greater peak than formula-fed newborns. Clinical examination will reveal icterus when total serum bilirubin levels

above five to six mg/dl. As the blood bilirubin level increases, the clinical icterus progresses in a cephalo-caudal direction.

As a result, icterus over the head and sclera is noticeable at low total serum bilirubin levels. The icterus spreads to the belly and extremities as the bilirubin level rises. Clinical examination is very subjective and is highly dependent on the observer's experience. A noninvasive transcutaneous bilirubinometer is now available to objectively evaluate skin colour. The transcutaneous bilirubin measurement is more reliable than the ocular assessment.

Preterm infants have more acute physiologic jaundice than their mature counterparts. The highest bilirubin levels in these newborns will occur around the fifth day of life. This delayed peak is most likely owing to preterm neonates' delayed maturation of UGT activity. Although preterm newborns' hepatic UGT activity maturation is delayed, it is quicker than in-utero maturation.

The Typical Jaundice Pattern in Newborns:[39,46,47]

Unconjugated bilirubin is excreted by the foetus via the placenta and maternal liver. The typical bilirubin level in umbilical cord blood after delivery is 1-2 mg/dL in the absence of foetal hyperbilirubinemia or maternal liver illness.

Jaundice in newborns may be healthy or pathological, depending on the quantity and cause.

Physiological Hyperbilirubinemia :

It's the jaundice induced by neonates' physiological immaturity in coping with elevated bilirubin production as a result of an immaturity in the liver's bilirubin excretory pathway during the peak of bilirubin production. Between the ages of 24 and 72 hours, jaundice appears. By 3 days of age, the level of total serum bilirubin (TSB) in the

newborns had climbed to the maximum of six to eight mg/dL, before declining.A increase of up to Twelve mg/dL is considered normal.

On the fifth day of life, the peak in preterm babies may be 10 to 12 mg/dL, with the possibility of climbing to Fifteen mg/dL without any specific bilirubin metabolism problems.

Pathological Hyperbilirubinemia :

Total serum Bilirubin levels in term neonates are considered abnormal if they surpass five mg/dl within 24 hours , ten mg/dL by 48 hours , and 12-13 mg/dL by 76 hours.Any TSB increase of more than 17 mg/dL should be considered pathogenic, demanding further testing and treatment options, such as phototherapy.

Clinical jaundice lasting more than 2 weeks in term babies and 3 weeks in preterm babies (prolonged jaundice), conjugated bilirubin with dark urine staining the clothes and light-colored stool, and conjugated bilirubin with dark urine staining the clothes and light-colored stool are all signs of pathological jaundice.

NEONATAL HYPERBILIRUBINEMIA CLASSIFICATION: [48,49]

CLASSIFICATION OF NEONATAL HYPERBILIRUBINEMIA: 48,49

I) Classification based on bilirubin conjugation

II) Classification based onthe time of Onset Jaundice

I)Bilirubin conjugation classification:

unconjugated (indirect hyperbilirubinemia)

conjugated (direct hyperbilirubinemia) (Direct hyperbilirubinemia)

II) The Begining of jaundice is used to classify the condition.

1. Within the first 24 hours, jaundice emerges.

2. Jaundice develops during the daytime two times a week, otherwise three times a week.

3. After the first week, jaundice emerges.

4. Jaundice that persists throughout the first 28 days.

I) Unconjugated (Indirect hyperbilirubinemia) is further classified as follows: a. Physiological jaundice; b. Intrinsic and extrinsic hemolytic causes; and c. Non-hemolytic causes.

d. Substances/disorders that affect the binding of bilirubin to albumin

a) Jaundice due to physiological causes Many neonates develop noticeable jaundice during their first week owing to an increase in unconjugated bilirubin levels.

Physiological jaundice is the name for this common illness.

o It is usually not present in the first 24 hours

o It sometimes climbs beyond 5 mg/dl in a 24 hrs

o Direct bilirubin will be usually less than 2 mg/dl.

A. **Term New born :**50-60% of neonates are jaundiced in the first week of life, and the total blood bilirubin level reaches its greatest range around 3–5 days. The amount of bilirubin in your blood should not be more than 13 mg/dl. After 14 days, it normally goes gone.

B**. Preterm newborns:**Preterm newborns are more likely than mature neonates to have visible jaundice. At the age of 5-7 days, total serum bilirubin reaches its greatest level. The bilirubin level in the blood should not exceed 15 mg/dl. After 21 days, it normally goes gone.

Neonates who do not meet the aforementioned criteria should be investigated and treated as if they had pathological jaundice.

Etiology of physiological jaundice

Preterm newborns are more prone to acquire visible jaundice than mature neonates. Total serum bilirubin reaches its highest level between the ages of 5-7 days and 14 days. The blood bilirubin level should not be more than 15 mg/dl. After 21 days, it usually disappears.

The enzyme has been carefully preserved at low levels in the foetus before delivery, since bilirubin must remain unconjugated in order to travel through the placenta and avoid accumulating. It takes a few days for the enzyme glucuronyl transferase to regain its function after delivery.

Adult red blood cells have a lifespan of 100 to 120 days, whereas children born at term have just 80 to 90 days. Due to insufficient conversion of bilirubin to urobilinogen by the gut flora, bilirubin is reabsorbed into the circulation.

There are two forms of jaundice in neonates who are breastfed. The majority of the time, neither category is harmful.

They are

i. Breastfeeding jaundice that appears early.

ii. Breast milk jaundice with a late onset

Breastfeeding Jaundice - Early Onset [50,51,52]

The newborns who are breast-fed are more susceptible to early-onset exaggerated physiologic jaundice when they have a significant energy deficit in the first few days of life. Low volume and quantity of feedings cause meconium passage delays as well as moderate dehydration.

Breastfed babies are three to five times more likely than formula-fed infants to be moderately or severely jaundiced .

Few neonates with decreased milk intake, as well as those with dehydration or a reduction in calorie intake, have higher bilirubin circulation in the enterohepatic system. The spike in enterohepatic circulation might be caused by a decrease in intestinal bacteria that converts bilirubin to non reabsorbed compounds.

Breast milk jaundice with a late onset[52]

Nursing-induced jaundice differs from breast milk-induced jaundice. Affected are newborns who are otherwise healthy, full-term, and breastfeed. In breastfed infants, it is characterised by indirect hyperbilirubinemia. It occurs during the fifth and seventh days of life, and by the second week, it has reached its height. It lasts a long time compared to regular jaundice.

The following factors contribute to it:

1. The stomach is devoid of infective organisms after birth, and the formation of normal gut flora takes longer. Adult gut bacteria convert conjugated bilirubin to stercobilinogen, which is expelled in the faeces.

2. Brush border-glucuronidase deconjugates bilirubin, which is subsequently reabsorbed, when there are insufficient bacteria. Enterohepatic circulation is the name for this kind of reabsorption.

3. Elevated absorption of bilirubin in the colon (enterohepatic circulation) in breastfed newborns is caused by increased amounts of a chemical called epidermal growth factor found in Breast milk.

4. The presence of glucuronidase in breast milk enhances bilirubin deconjugation and enterohepatic recirculation.

5. Certain mothers' breast milk contains 3-alpha-20-beta pregnanediol, a progesterone metabolic product. Pregnanediol suppresses the activity of the uridine diphosphoglucuronic acid glucuronyl transferase, which is prone to bilirubin conjugation and removal.

6. Because glucuronyl transferase activity in the infant's liver is just 0.1-1 percent of that in an adult, bilirubin conjugation is diminished. Bilirubin levels in the blood rise when bilirubin conjugation is inhibited.

7. Lipoprotein lipase, an enzyme found in breast milk, inhibits hepatic glucuronyl transferase, resulting in decreased conjugation and bilirubin excretion.

In July of 2004, the American Academy of Pediatrics published procedures that would reduce the occurrence of preventable conditions. [2]

Successful breastfeeding should be advocated for each infant delivered by 35 weeks or more of pregnancy, according to the AAP Subcommittee on Hyperbilirubinemia.

In July of 2004, the American Academy of Pediatrics published procedures that would reduce the occurrence of preventable conditions. 2

Successful breastfeeding should be advocated for each infant delivered by 35 weeks or more of pregnancy, according to the AAP Subcommittee on Hyperbilirubinemia:

Recommendation 1: For the first few days, doctors should urge mothers to breastfeed their babies at least eight to ten times a day.

Recommendation 1.1: The American Academy of Pediatrics recommends avoiding administering water or (sugar) dextrose water to non-dehydrated breastfed neonates on a regular basis.

o Hereditary elliptocytosis o Hereditary spherocytosis o RBC membrane deficiencies

Defect in globin synthesis

o Thalassemia is a kind of anaemia.

sickle cell anaemia is a kind of anaemia that occurs when a person's blood

Situations that are systemic

o Extrinsic Sepsis o Arteriovenous malformation

o Incompatibility with Kell o Incompatibility with ABO

o Alloimmunity (positive Coomb's test from the cord or neonate, as well as a positive indirect Coomb's test from maternal blood)

o Incompatibility with Rhc

o Other blood type mismatches that result in hemolysis in the infant.

Incompatibility with Rh

b) Causes other than hemolysis

I Reduced hepatic bilirubin absorption and conjugation Jaundice in breast milk

Diabetic Mothers' Infants

Criggler Najjar Syndrome

pyloric stenosis

Gilbert Syndrome hypothyroidism

In all babies, glucuronyl transferase activity is immature.

ii) Increased reabsorption in the enterohepatic system Blockage of the bowels There will be no enteric feedings. Breast-feeding causes jaundice .

d) Substances/disorders that affect bilirubin-albumin binding fatty acids in dietary products.

Conjugated (B) (Direct Hyperbilirubinemia)

The following features explains pathological jaundice:

a) Direct bilirubin levels more than 34 mol/l.

b) The initial 24 hours of sickness are marked by clinical jaundice.

c) A increase in total bilirubin concentration of greater than 8.5 mol/l (0.5 mg/dL) every hour or (85 mol/l) 5 mg/dL per day.

d) Levels of total bilirubin more than 331.5 mol/l (19.5 mg/dL).

II) The start of jaundice is used to classify the condition.

1)Jaundice arises during the first 24 hours:

Pathological jaundice is caused by erythroblastosis fetalis.

Extravascular hematoma is a kind of hematoma that occurs outside of (TORCH) Infection in the uterus (TORCH) Sepsis

2)Jaundice arises on the second or third day:

Syndrome of Criggler-Najjar Physiological jaundice is a kind of jaundice that occurs when the body Early-onset jaundice from breast-feeding

3)Jaundice occurs after the first week:

• Hypothyroidism • G6PD deficiency • Galactosemia • Breast milk jaundice • Extrahepatic biliary atresia

4) Jaundice that persists beyond the first month:

• Hyperalimentation • Congenital infection • Inspissated biliary syndrome

The pathophysiology of infant jaundice is complicated by increased bilirubin production and decreased bilirubin conjugation. Although many infants are born with natural jaundice, a variety of risk factors might affect the severity and duration of hyperbilirubinemia.[53]

When mutations in the gene coding for UDP-glucuronosyl transferase 1A1 (UGT1A1) are present in combination with other risk factors, the frequency and severity of neonatal jaundice is increased.[54]

Clinical Examination of Jaundice:[55,56]

Bilirubin skin staining in newborns, according to Kramer, might be used as a crude clinical reference for the amount of jaundice. Because of the variation in the quantity of subcutaneous tissue in newborns, skin staining proceeds in a cephalo-caudal direction.

In broad daylight, the neonate should be inspected. The underlying colour of the skin and subcutaneous tissues may be seen by blanching the skin with digital pressure. In babies with yellow discolouration of the soles, TSB levels should be checked as soon as possible. If a newborn has had phototherapy, the skin is blanched, and if the infant has dark skin, it may mask jaundice; clinical evaluation is not particularly trustworthy and accurate if a newborn has had phototherapy, as the skin is blanched, and if the infant

has dark skin, it may mask jaundice; clinical evaluation is not particularly trustworthy and accurate if a newborn has had phototherapy, as the skin is blanched, and if the infant has dark skin, it may mask jaundice; For screening, a transcutaneous bilirubinometer may be utilized.

Diagnosis of Unconjugated Hyperbilirubinemia[2]

Two out of every three newborns will have clinical jaundice, however the percentage of infants who suffer severe jaundice will be lower. The pediatrician's job is to identify newborns who are at danger of developing severe jaundice. The American Academy of Pediatrics (AAP) has recommendations for evaluating newborns with jaundice.

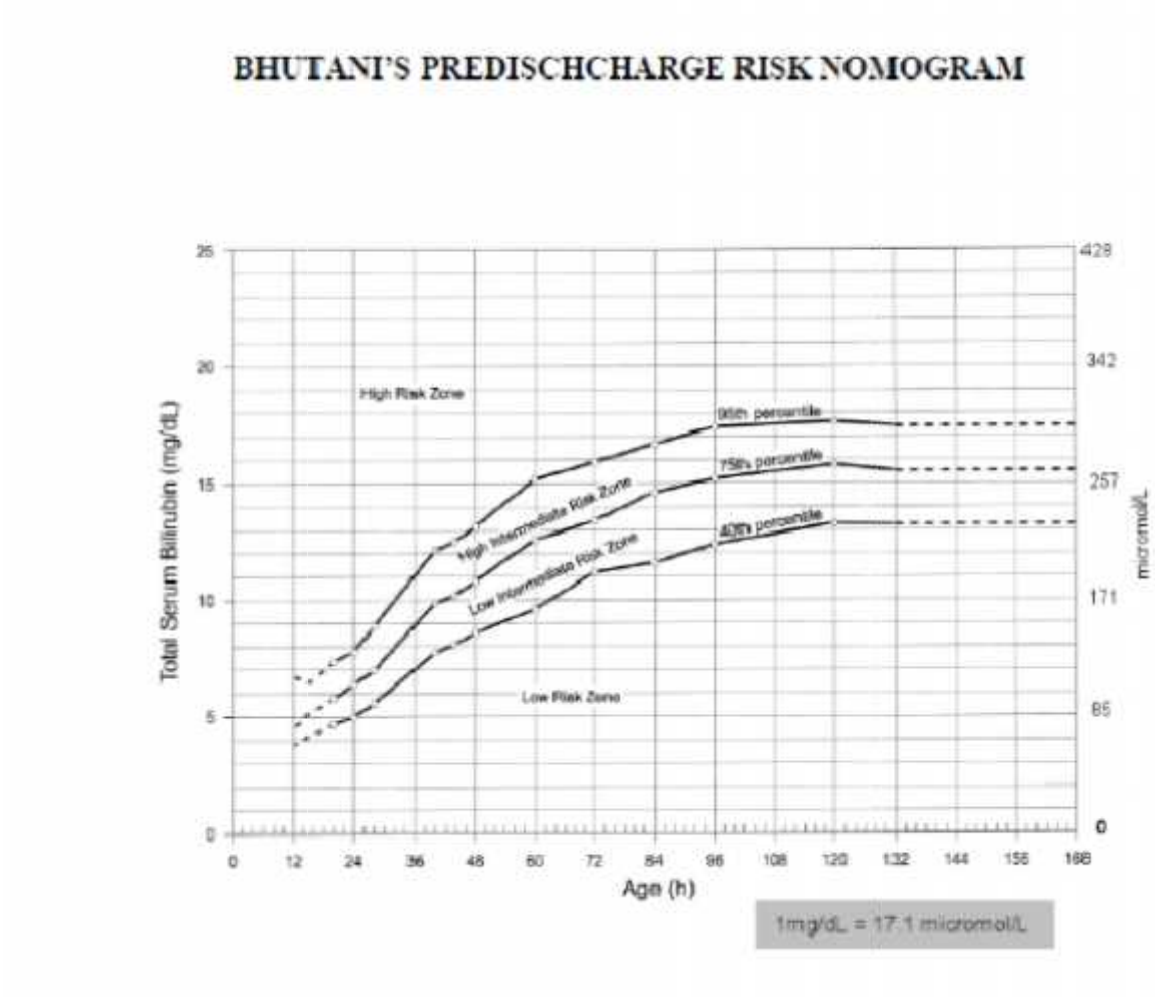
Total Serum Bilirubin measurement: [2,3,8]

When a neonate is clinically diagnosed with jaundice, a total serum bilirubin test should be performed. The direct fraction of bilirubin has not been proved to be beneficial in early stages, but it must be assessed in newborns with chronic jaundice and in babies who are suspected of having direct hyperbilirubinemia. Repeat serum bilirubin measurements are required in the majority of newborns to determine the trajectory and to guarantee that the threshold level for starting therapy has not been achieved. It is often required to assess serum bilirubin on a daily basis until the decreasing trend in serum bilirubin is verified.

It is crucial to assess a newborn clinically and determine if bilirubin monitoring may be performed as an outpatient procedure or whether hospitalisation is required. As a result, newborns should be classified as low risk or high risk based on their likelihood of having severe jaundice.

Babies with jaundice that lasts less than 24 hours, hepatosplenomegaly, or hemolysis are thought to be at a greater risk of developing severe hyperbilirubinemia.

Bhutani et al.,[57] developed an hour-specific bilirubin normogram of predischarge total bilirubin concentration to predict the likelihood of severe hyperbilirubinemia. A infant with a pre-discharge serum bilirubin in the high risk zone (95th percentile) has a 57 percent chance of developing severe jaundice. A infant with serum bilirubin in the high intermediate risk zone (75th to 95th percentile) has a 13 percent danger, whereas a baby with serum bilirubin in the low intermediate risk zone faces a 2.1 percent risk (40th to 36 75th centile). There is no danger of severe jaundice in an infant whose pre-discharge bilirubin is in the low risk zone (40th percentile). Although the danger of severe jaundice is nearly zero if the pre-discharge serum bilirubin is in the low-risk zone, the American Academy of Pediatrics advises that all newborns be followed up on within a few days after release. To determine the trajectory, repeat serum bilirubin should be plotted on the normogram. If the serum bilirubin level rises from a lower to a greater danger zone, it should be taken seriously and more investigation is required.



The methods for estimating bilirubin should also be considered. The most reliable technique for estimating serum bilirubin is high-performance liquid chromatography (HPLC). Other approaches may, to variable degrees, underestimate the serum bilirubin level.

A neonate with hyperbilirubinemia should be evaluated further if the cord blood bilirubin level is >4 mg/dl, the rate of bilirubin rise is more than 0.5 mg/dl/hour over a period of 4-8 hours, the rate of rise is more than 5 mg/dl/ day, the serum bilirubin level has increased to more than 15 mg/dl in a term neonate, more than 10 mg/dl in a pre 57

In a newborn with hyperbilirubinemia, second-line investigations should be based on the history and physical examination. The pattern of eating and a full family history

should be included in the history to rule out a hereditary cause of hyperbilirubinemia. A thorough assessment of neurological state and organomegaly for hemolytic causes should be included in the physical examination.

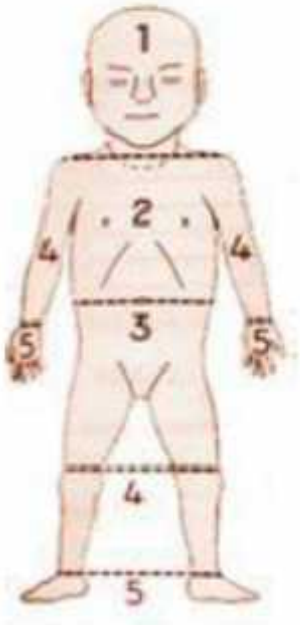
Maternal blood grouping and type, direct Coombs test, haemoglobin, blood smear for RBC shape, and reticulocyte count should all be part of the first laboratory evaluation. The direct Coombs test should be performed at least once in neonates with ABO incompatibility since it might be negative at first, even if there is evidence of hemolysis.

In hemolytic circumstances, end tidal carbon monoxide (ETCO) will be high, although it is not easily accessible. In certain newborns with unexplained jaundice and hemolysis, a G6PD test may be ordered. Other tests, such as enzyme studies and genetic testing, might be reserved for newborns with persistent hyperbilirubinemia who meet certain criteria.

A liver function test should be included in the investigation package for newborns with conjugated hyperbilirubinemia. Total blood bilirubin, gestational age, and indications of hemolysis are all factors to consider when evaluating a neonate's risk of developing bilirubin encephalopathy. The American Academy of Pediatrics (AAP) advises starting therapy for neonates who are more than 35 weeks pregnant. [2]

Unbound serum bilirubin levels may be a more definitive indication for determining a child's risk of encephalopathy. According to studies, the concentration of unbound bilirubin correlates better with bilirubin encephalopathy than total serum bilirubin. [58,59]

KRAMER'S GUIDE



Area of the body	Level of bilirubin
1.Face	4-6 mg/ dl
2.Chest, upper abdomen	6-10 mg/dl
3.Lower abdomen, thighs	10-12 mg/dl
4.Arms, legs	12-15 mg/dl
5.Palms, soles	>15 mg/dl

Treatment:[60,61]

Phototherapy and a double volume blood exchange transfusion are the two most popular treatments for babies with hyperbilirubinemia. Phototherapy converts insoluble unconjugated bilirubin into water soluble molecules that may be eliminated in urine and faeces.

By eliminating 80-85 percent of circulating RBCs and lowering the bilirubin burden can be done by Double Volume Blood Exchange Transfusion (DVET) . [13,19]

The American Academy of Pediatrics (AAP) separates babies into two groups: those who are 35 weeks pregnant and those who are more than 35 weeks pregnant.

The following recommendations should be followed by newborn newborns under 35 weeks of gestation: The American Academy of Pediatrics (AAP) published [14,62] charts

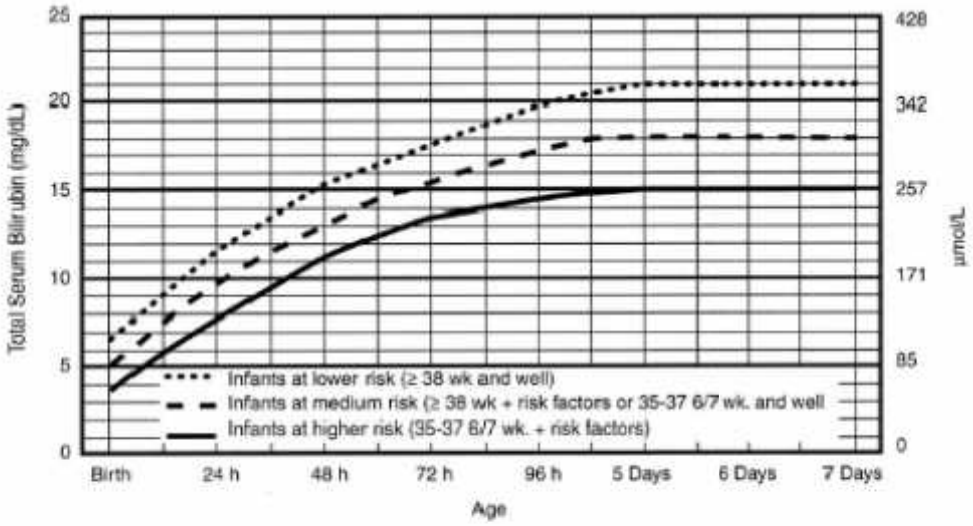
for PT and Double Volume Exchange Transfusion (DVET) for newborn infants under 35 weeks of gestation in 2004.

For newborns delivered beyond 35 weeks of pregnancy, the following guidelines apply: [14]

As shown in the table below, the Maisels charts are widely used to establish the cutoff for phototherapy and exchange transfusion for premature neonates under 35 weeks of gestation.

Premature infants (those born before 35 weeks of pregnancy) should be treated as soon as possible.[14]

AAP GUIDELINES FOR PHOTOTHERAPY FOR NEWBORNS >35 WEEKS OF GESTATION



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Phototherapy and exchange transfusion have the following adverse effects.

Side Effects of Phototherapy

Diarrhea

Increased evaporation of fluid via the skin

Instability of temperature

Rashes with erythematous rashes

Tanning

Syndrome of the bronze-baby

Damage to the retina

Male infants with testicular injury

Consequences of an exchange transfusion

Infections transmitted via the blood

Accidents involving the blood vessels

Problems with the heart

Disruptions in biochemistry

Disturbances in the haematological system.

Adjunctive treatments:

In a few trials, phenobarbitone, fluid supplementation, and IVIG have showed promise in lowering severe hyperbilirubinemia, however further data is needed.

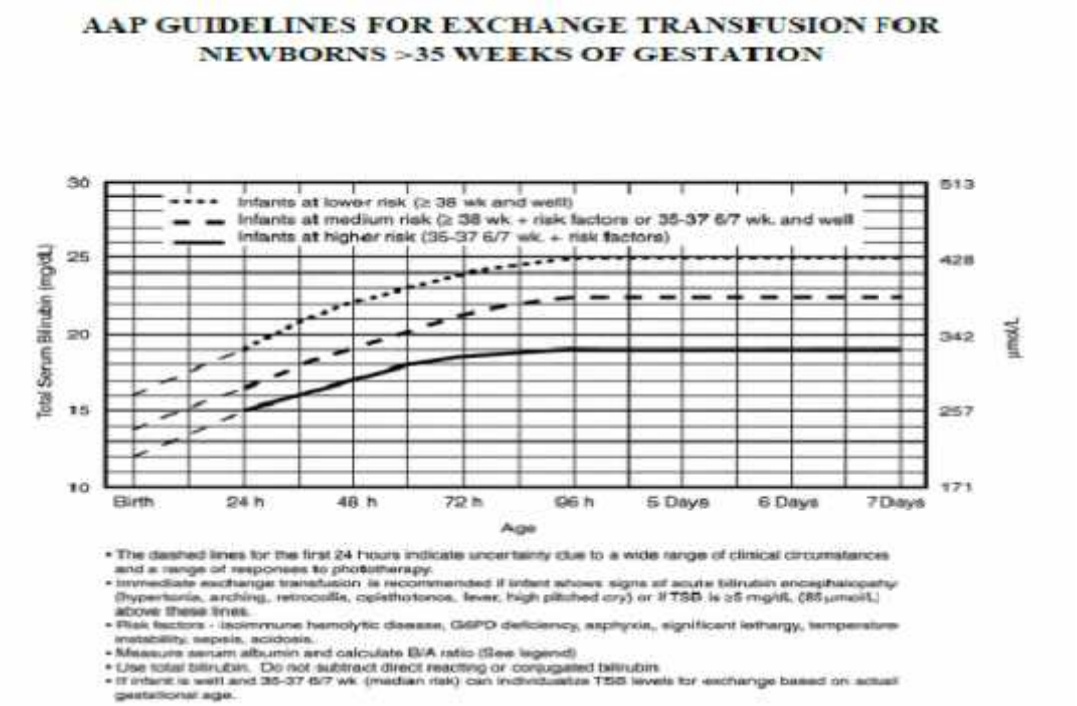
Phenobarbitone:

It helps reduce bilirubin levels by increasing the activity of the uridine-diphosphate glucuronyl transferase (UDPGT) enzyme. In a few trials, it has been demonstrated to be beneficial [23-26]

Fluid Supplémentation : Intravenous and oral fluid supplements have been demonstrated to improve the clearance of water soluble photo-products of bilirubin produced during phototherapy in severe hyperbilirubinemia caused to subclinical dehydration.[16]

IVIG: IVIG treatment reduces hyperbilirubinemia caused by ABO and Rh incompatibility by producing non-specific inhibition of Fc receptors in the reticuloendothelial system and slows hemolytic breakdown of red blood cells. [63,64]

Boo and Lee [65] studied how blood bilirubin levels fell in severely jaundiced but healthy term neonates who were given 10% of their daily maintenance fluids as either oral or intravenous fluid supplementation during phototherapy. They found that whether extremely jaundiced healthy term newborns got oral or intravenous fluid supplementation, the rate of decline in unconjugated bilirubin levels during the first 4 hours of strong phototherapy was the same. According to the researchers, all healthy term neonates with severe and considerable hyperbilirubinemia who need extended phototherapy should get all of their maintenance and extra fluid by enteral feeding. They discovered that the rate of decline in blood bilirubin in their newborn children was 0.6 mg/hour for the oral group and 0.65 mg/hour for the intravenous group within the first four hours after birth.



According to the American Academy of Pediatrics, strong phototherapy should reduce blood bilirubin levels by 1–2 mg/dL within 4 hours of treatment to be effective. In Boo and Lee's trial, the faster rate of decline in blood bilirubin, which was higher than the American Academy of Pediatrics' recommendation, might be attributed to more effective phototherapy illumination and/or fluid supplementation. However, they recommended that a larger sample size be used in a comparable research to identify a smaller significant difference in the rate of blood bilirubin decline between oral and intravenous fluid replenishment procedures. The absence of a control group to compare to the two ways of fluid supplementation in order to ascertain whether fluid supplementation was even effective in the first place hampered their research.[2]

Sixty healthy term breast-fed newborns with non-hemolytic hyperbilirubinemia were randomly randomised to receive either breast milk alone or intravenous fluid in

addition to the breast milk during conventional phototherapy in a research conducted by Iranpour et al [66]. The mean total blood bilirubin levels at the time of enrollment and 84 hours following phototherapy were not significantly different between the two groups, according to this research.

Mehta et al [16] carried out a 74-baby randomised controlled trial of fluid supplementation in term healthy newborns with severe hyperbilirubinemia. They were divided into two equal-sized groups. Group 1 received phototherapy and regular feeding (Control). In addition to the regular Feeds, Group 2 (Extra fluid) received phototherapy. Extra fluids included IV fluid supplementation with N/5 (0.2 percent) saline in 5% dextrose for an 8-hour period during phototherapy. The supplement included a 50 mL/kg shortfall (equivalent to mild dehydration), half of daily maintenance requirements for an 8-hour period, as per recognised standards, and a phototherapy allowance of 20 mL/kg/day. The babies were then given supplementary oral feeding of 30 mL/kg/day (either expressed breast milk or formula) until phototherapy was terminated. Phototherapy was ceased when two TSB values obtained at least 12 hours apart were less than 15 mg/dL.

If TSB rose by 2 mg/dL after 4 hours or stayed below 20 mg/dL after 8 hours, an exchange transfusion was performed. Fluid supplementation reduced the incidence of exchange transfusion and the duration of phototherapy in term infants with severe hyperbilirubinemia, according to their findings.

Fluid supplementation, on the other hand, significantly reduced the rate of exchange transfusion and phototherapy duration in patients with serum osmolality >290 mOsm/kg compared to patients fed exclusively with breast milk who also had serum osmolality of >290 mOsm/kg; fluid supplementation, on the other hand, did not

significantly reduce the rate of exchange transfusion and phototherapy duration in patients with serum osmolality 290 mOsm/kg.

Reza Saeidi et al [67] conducted a study at Ghaem Hospital in Mashhad, Iran, from October 2007 to April 2008 to see whether intravenous extra fluid treatment may speed up the eradication of jaundice in infants undergoing phototherapy. They gathered 100 fully developed, jaundiced babies with total bilirubin levels of 18 mg/dl or above. Patients were randomly assigned to one of two groups during phototherapy: group I (case group) received supplemental parenteral fluids in addition to breast feeding, whereas group II (control group) received just breast milk. The rate of bilirubin depletion, the length of stay in the hospital, and the rate of blood exchange were all compared. The extra fluid was given to a 2-day-old baby at a rate of 80 cc/kg of 1/5 normal saline in 5% dextrose, with an additional 10 cc/kg each day after that, up to a maximum of 120 cc/kg delivered through the peripheral vein during the first 24 hours. Both groups received the same phototherapy, which comprised of fluorescent lamps shining at a 25-centimeter distance. They detected a statistically significant decline in serum bilirubin levels in the first 24 hours. There was no significant difference between the two groups in terms of exchange transfusion rates. Extra parenteral fluid administration may hasten the decrease of blood bilirubin levels in icteric babies in the first 24 hours, according to the researchers

. The Saini et al [68] study included data from two previous randomised controlled trials of fluid supplementation in full-term babies with severe non-hemolytic hyperbilirubinemia (one published and one unpublished). Fluid supplementation was given to one group of 121 newborns with severe jaundice, whereas the other received just oral feeding. According to the researchers, fluid supplementation for severe non-

hemolytic hyperbilirubinemia is less likely to be effective in neonates delivered by caesarean/instrumental birth than in normal vaginal birth.

Demirsoy et al [69] studied Zeynep's newborn critical care section at Kamil Maternity and Children Hospital for four months (Istanbul, Turkey). 250 healthy term babies with hyperbilirubinemia were randomly assigned to either breast milk alone (n=125) or breast milk plus intravenous fluid (n=125) during phototherapy.

According to the results of this study, intravenous fluid supplementation had no effect on the rate of reduction in blood bilirubin or the time of phototherapy treatment in healthy term babies.

Hazem A Al-Masri [70] conducted study during phototherapy to investigate the effectiveness of fluid supplementation in jaundiced healthy term babies. A prospective study was conducted by researchers from Prince Hashim Hospital and King Hussein Medical Centre between September 2008 and November 2009. (KHMC). A total of 80 healthy term breast-fed and formula-fed neonates with hyperbilirubinemia were randomly assigned to one of two groups: the first received just oral feeds (n=40), while the second received intravenous fluid as well as oral feeds (n=40). The extra fluid given to the supplemented group was equivalent to 20% of the quantity given to the control group. There were no significant variations in the mean gestational age, weight, or indirect serum bilirubin level between the two groups when they were admitted to the hospital. The mean TSB levels in the two groups were not substantially different 72 hours after phototherapy. The researchers found that in healthy term newborns with hyperbilirubinemia, there is no need to add more fluid during phototherapy, and that the

harmful effects of intravenous cannulation may be avoided by simply using oral feeding..

Balasubramanian et al. [71] evaluated the incidence of hyponatremia in full-term newborns with severe hyperbilirubinemia who received intravenous fluid supplementation with either 0.2 percent saline in 5% dextrose or 0.9 percent saline in 5% dextrose to prevent blood exchange transfusions (BET). This double-blind, randomised, controlled study comprised fullterm newborns (37 weeks), who were appropriate for gestational age and had severe non-hemolytic hyperbilirubinemia (serum bilirubin >20 mg/dL). During an 8-hour period, eligible neonates were randomly assigned to receive either 0.2 percent saline in 5% dextrose (hypotonic fluid group) or 0.9 percent saline in 5% dextrose (isotonic fluid group) in addition to standard phototherapy.

At a Randomised controlled experiment done in a tertiary care hospital in North India in 2014, neonates were randomly assigned to one of three research groups in a 1:1:1 ratio: The rate of decline of STB (Serum total bilirubin) was substantially quicker in the IV fluid group throughout the 8-hour intervention period than in the oral fluid group or the control group (DBF Only). [72]

The Cochrane group (2017) conducted a metaanalysis of seven papers and concluded that further research should be done in diverse populations and in babies who are at risk of dehydration. [73]

MATERIALS AND METHODS:

Study Center :

Department of Pediatrics, J N Medical College and Hospital, Belgaum's KAHER Dr Prabhakar Kore Hospital NICU, where neonates hospitalised with Physiological Hyperbilirubinemia were studied.

Randomized Controlled Trail Study was used as the study design. The project will run from June 2020 until May 2021.

Subjects include:

The research will cover neonates born in a hospital at 34 weeks+1 day or more of gestation and hospitalised with hyperbilirubinemia (any infant in the phototherapy range). Enrolled newborns were randomly assigned to one of two research groups: oral fluid supplementation (oral rehydration solution) or the control group in a 1:1 ratio. One of the two groups got 50 millilitres per kilogramme of additional fluids (double dilution) and breast milk. Over the course of 16 hours, ORS was delivered in 8 split feeds.

Sample size :

G*Power software is used to determine sample size. In the research, there were two groups. At three separate time points, data will be gathered (at admission, at 24 hours, at 48 hours). By assuming a middle effect size of 0.2, a 5% level of significance, an 85 percent power level, a non-sphericity correction of 1 and a 0.3 correlation between repeated measurements, a sample size of 33 participants per group (total sample sizes necessary 332=66 samples) was achieved.

Data Collection :

The research will involve neonates delivered in the hospital at 34 weeks+1day or more of gestation and hospitalised with hyperbilirubinemia (any infant in the phototherapy range). Need for intensive care for additional morbidities, significant congenital deformity, STB (Serum Total Bilirubin) at admission greater than threshold for exchange transfusion, clinical symptoms of dehydration requiring intravenous fluid therapy will be excluded from the trial. Based on a computer-generated random

number, the research volunteers were separated into study and control groups. Enrolled neonates will be assigned to one of two research groups: oral fluid supplementation (oral rehydration solution (ORS)) or a control group in a 1:1 ratio. The group assignments will be maintained in serially numbered sealed opaque envelopes that will be unsealed when approval for enrolment is obtained. The lead investigator will be in charge of assigning the intervention. One of the two groups will get 50ml/kg additional fluids (dilution twice) as well as breast milk. The Performa will be used to monitor bilirubin levels and electrolytes.

Inclusion Criteria :

Late preterm and Term neonates who are in phototherapy range.

Exclusion Criteria :

1. Infants having STB levels over the threshold for exchange transfusion at the time of admission.
2. Bilirubin encephalopathy (acute bilirubin encephalopathy) (kernicterus)
3. Dehydration symptoms that are obvious (i.e., sunken fontanel, reduced skin turgor, dry mucosa, tachycardia, delayed capillary refill, excessive weight loss)
4. Congenital abnormalities of major importance
5. Infants who are already getting intravenous (IV) fluids.

Data Collection and Monitoring:

The study participants were divided into study and control groups using a computer-generated randomization approach, in which numbers were assigned to study and control groups at random. At the start of the study, the recruited newborns' body weights, hydration condition, and feeding data were documented. At enrolment, blood samples were taken for serum sodium, DCT, STB, renal function tests, hematocrit, and

reticulocyte count. In both groups, serum sodium and STB were tested again after 24 hours. At 48 hours, STB was tested once again.

A rebound STB value was also measured 12 hours after phototherapy was stopped. Body weight, hydration status, feeding details, fluid intake, urine output, stool frequency, and clinical indicators of bilirubin encephalopathy were all assessed daily in the neonates. The babies were continuously followed until they were released from the hospital.

Proforma for Data Collection:

Data was gathered using the proforma provided in the annexure.

Statistical Analysis:

SPSS software version 21 for Windows was used to conduct all statistical analyses using the intention to treat principle (SPSS Inc., Chicago, IL, USA). The data was imported into a Microsoft Excel spreadsheet and analysed using the SPSS 22 programme. Frequencies and percentages were used to represent categorical data. For qualitative data, the Chi-square test / Pooled chi square was utilised as a test of significance. The mean and standard deviation were used to describe continuous data. For continuous variables, the Student T test was employed to determine the degree of significance between two groups.

Data visualisation: MS Excel and MS Word were used to create a variety of graphs, including bar diagrams, pie diagrams, and line diagrams. After applying all statistical procedures, a p value (probability that the result is true) of 0.05 was judged statistically significant.

Results:

Table 1 : Distribution of sociodemographic variables among the study subjects

		Group				P Value
		Case (n=33)		Control(n=33)		
		N	%	N	%	
Gender	Male	16	48.5%	15	45.5%	Chi Square=0.061 P= 0.805
	Female	17	51.5%	18	54.5%	
Mean Birth Weight		2921.82±437.30		2706.36±407.19		0.042
Delivery	Normal	3	9.1%	3	9.1%	
	LSCS	30	90.9%	30	90.9%	

In the present study in the case group nearly 48.5% of the newborns were male and 51.5% were female and in the control group 45.5% were male and 54.5/5 were female. The association between the gender and its distribution between the groups was found to be statistically insignificant with p value of 0.805.

The mean Birth weight of study subjects in the case group was 2921.82±437.0 gms and in the control group it was 2706.36± 407.19 gms and its association was found to be statistically significant with p value of 0.042.

In both the study groups 9.1% of them were delivered by normal delivery and 90.9% were delivered by cesarean section in the present study .

Figure 1: Graph wise distribution of study subjects based on gender in both the groups

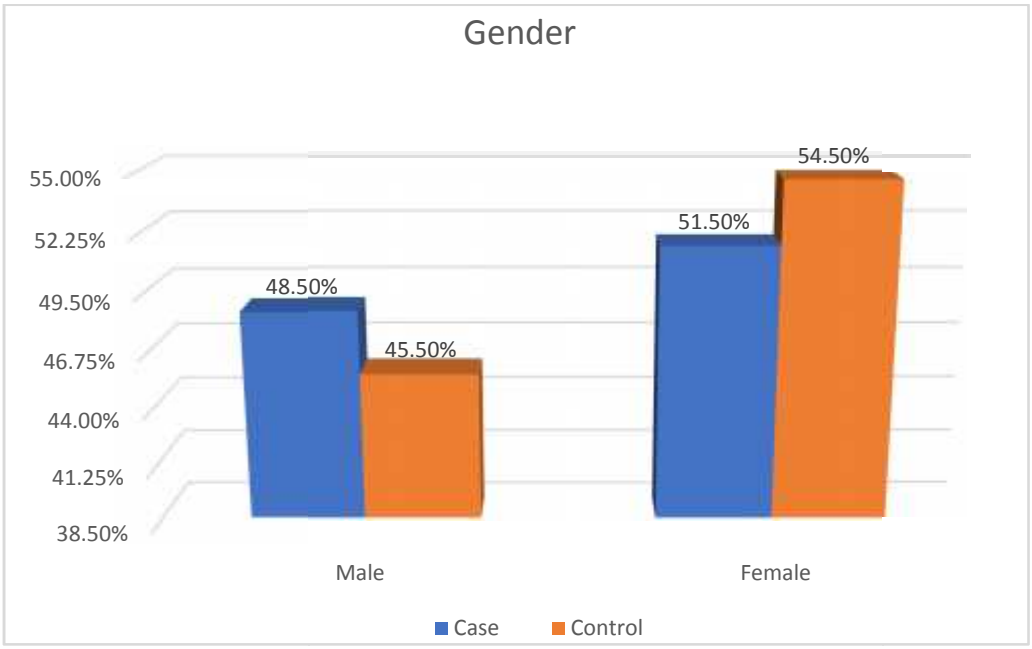


Figure 2: Graph wise distribution of study subjects based on Birth Weight in both the groups

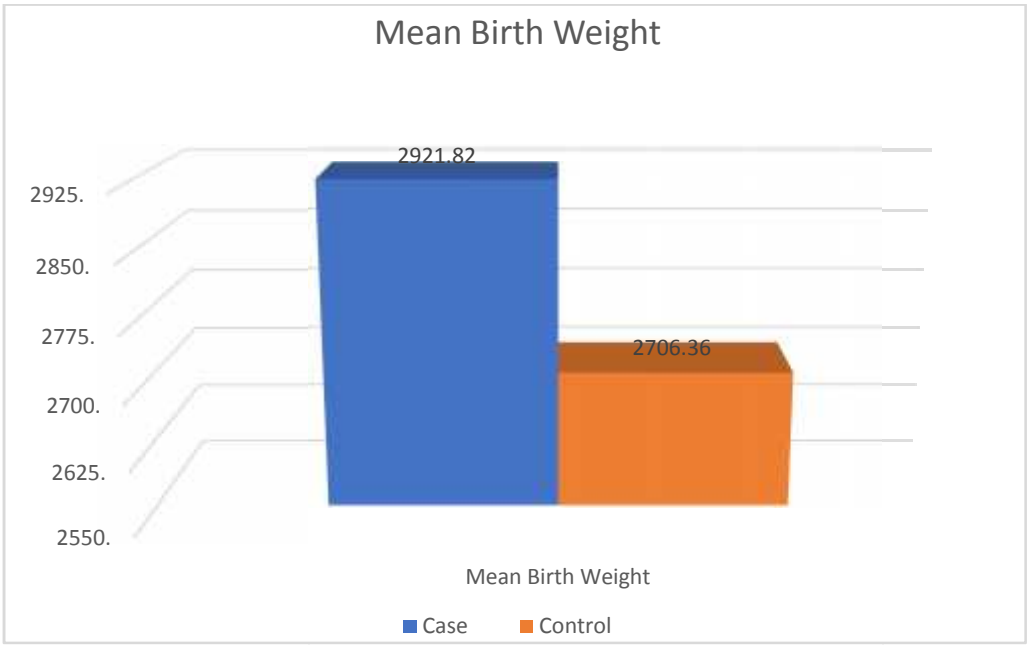


Figure 3 : Graph wise distribution of study subjects based on Mode of Delivery in both the groups

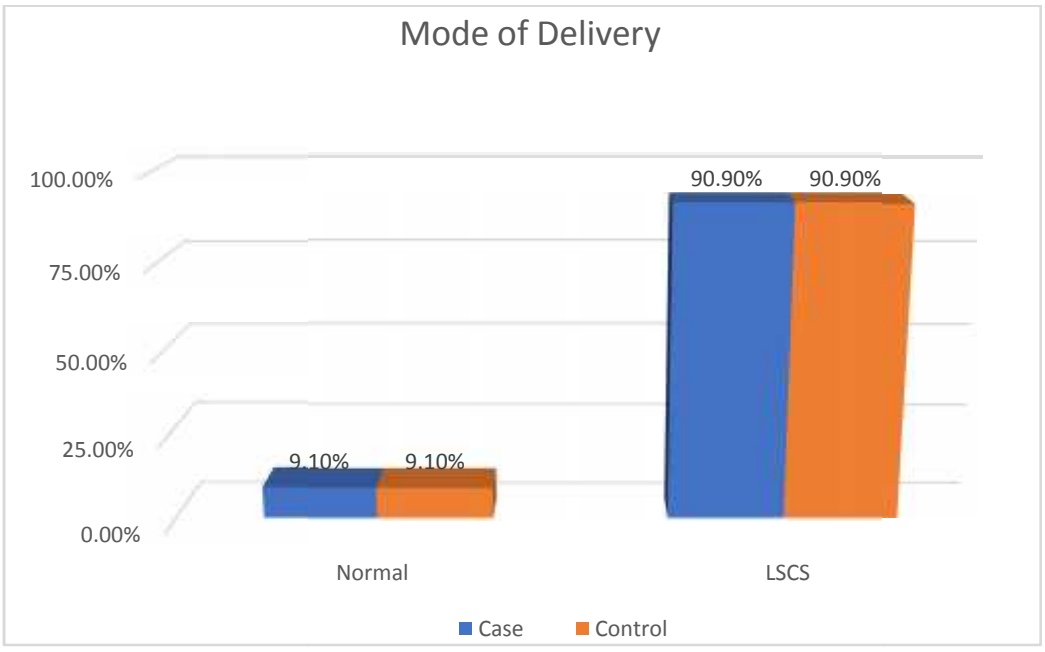


Table 2: Distribution of Risk Factors for NNH at the time of admission

	group	P Value

		Case		Control		
		Count	Column N %	Count	Column N %	
Mother's Blood group	A +	8	24.2%	9	27.3%	Chi Square = 3.225 P=0.780
	A -	1	3.0%	2	6.1%	
	B +	4	12.1%	8	24.2%	
	B -	1	3.0%	1	3.0%	
	O +	15	45.5%	9	27.3%	
	O -	2	6.1%	2	6.1%	
	AB -	2	6.1%	2	6.1%	
DCT	Negative	31	93.9%	33	100.0%	Chi Square = 2.063 P=0.151
	Positive	2	6.1%	0	0.0%	
Hemolysis	No	33	100.0%	33	100.0%	
Age at admission (hrs.)		82.36± 29.3		86.52 ± 35.78		0.608

In the present study the maternal blood group were compared between both the groups and it was found that in the case group 45.5% of them had O Positive , 24.2% had A Positive,12.1% had B Positive and 3% had A Negative, 3% had B Negative, 6.1% had O Negative and 6.1% had AB Negative Blood Groups . Among the control Group A Positive blood group was seen in 27.3%, O positive was seen in 27.3%, B positive in 24.2%, A Negative in 6.1%, O Negative in 6.3%, AB Negative in 6.3% and B Negative

was seen in 3% of the study subjects in Control Group. The Blood group was found to be statistically insignificant between both the groups .

In our study the direct Coomb's test was found to be Positive in 6.1% of study group and 0% in Control group. The negative Coombs test was seen in 93.9% in Control and 100% in group group. The association between DCT and the groups was found to be statistically insignificant.

All the study subjects in both the groups there was no hemolysis .The Mean age at the time of admission to hospital was for the purpose of treatment was found to be 82.36± 29.3 hours in the case group and 86.52±35.78 hours in control group and the association was found to be statistically insignificant .

Figure 4 : Graph wise distribution of study subjects based on Blood Group in both the groups

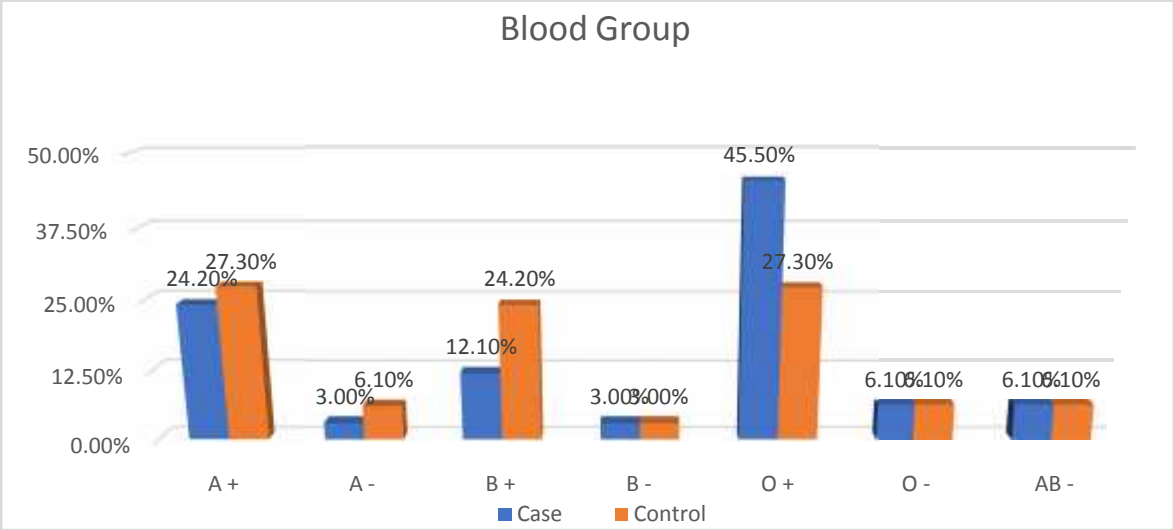


Figure 5 : Graph wise distribution of study subjects based on DCT in both the groups

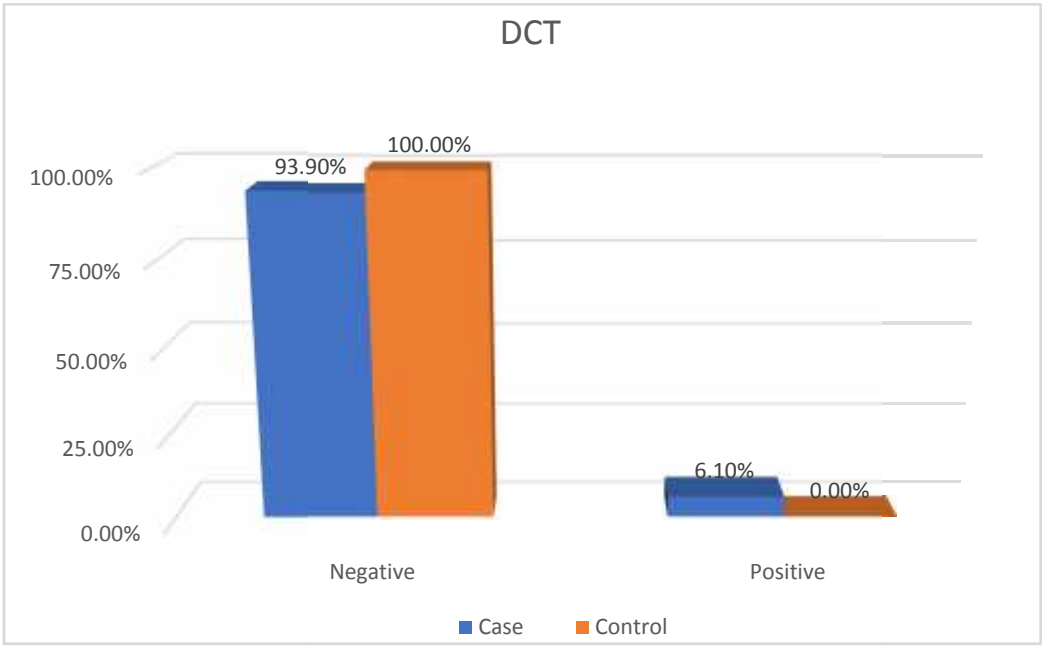


Figure 6: Graph wise distribution of study subjects based on Age at admission in both the groups

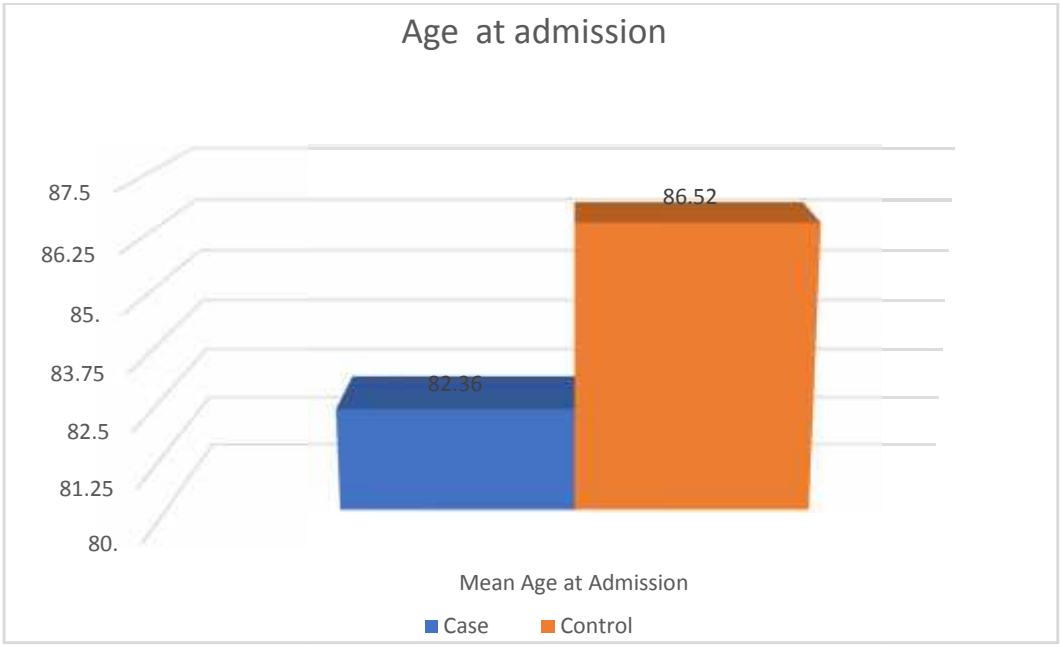


Table 3: Comparison of Total Serum Bilirubin and Direct Bilirubin among study subjects in both the groups

		group				P Value (Independent t test)
		Case		Control		
		Mean	Standard Deviation	Mean	Standard Deviation	
Total Serum Bilirubin (mg/dL)	At Admission(A)	17.18	3.20	15.91	2.70	0.085
	At 24 Hrs (B)	11.91	3.61	12.27	2.58	0.639
	At 48 Hrs (C)	9.76	2.49	9.73	2.23	0.959
Direct Bilirubin (mg/dL)	At Admission(A)	.58	.50	.55	.51	0.808
	At 24 Hrs (B)	.82	.53	.73	.45	0.455
	At 48 Hrs (C)	.76	.50	.67	.48	0.454

In the present study the total serum bilirubin levels were compared with study subjects in both the groups . At the time of admission, the mean total serum bilirubin was

17.18+ 3.20 mg/dl in study group and 15.91+ 2.70 in control group. After 24 hours post admission the mean total serum bilirubin level was 11.91+ 3.61 mg/dl in study group and 12.27+ 2.58 mg/dl and after 48 hours the mean total serum bilirubin was 9.76+ 2.49 mg/dl in study group and 9.73+ 2.23 mg/dl in control group . The association was found to be statistically insignificant for Mean total Serum Bilirubin between both the groups at the time of admission , 24 hours and even at 48 hours post admission.

In the present study the Direct bilirubin levels were compared with study subjects in both the groups . At the time of admission, the Direct bilirubin was 0.58+ 0.5 mg/dl in study group and 0.55 + 0.51 in control group. After 24 hours post admission the mean Direct bilirubin level was 0.82+ 0.53 mg/dl in study group and 0.73 + 0.45 mg/dl and after 48 hours the mean Direct bilirubin was 0.76 + 0.50 mg/dl in study group and 0.67 + 0.48 mg/dl in control group . The association was found to be statistically insignificant for Mean Direct Bilirubin between both the groups at the time of admission , 24 hours and even at 48 hours post admission.

Figure 7 : Graph wise distribution of study subjects based on Total Sérum Bilirubin **in both the groups**

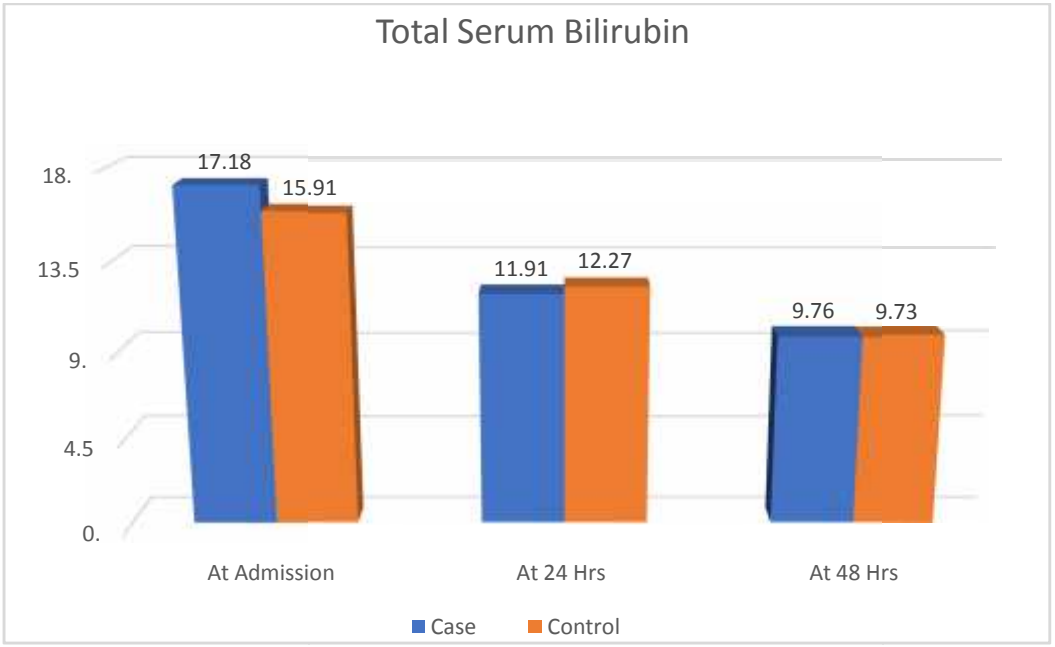


Figure 8 : Graph wise distribution of study subjects based on Direct Bilirubin in both the groups

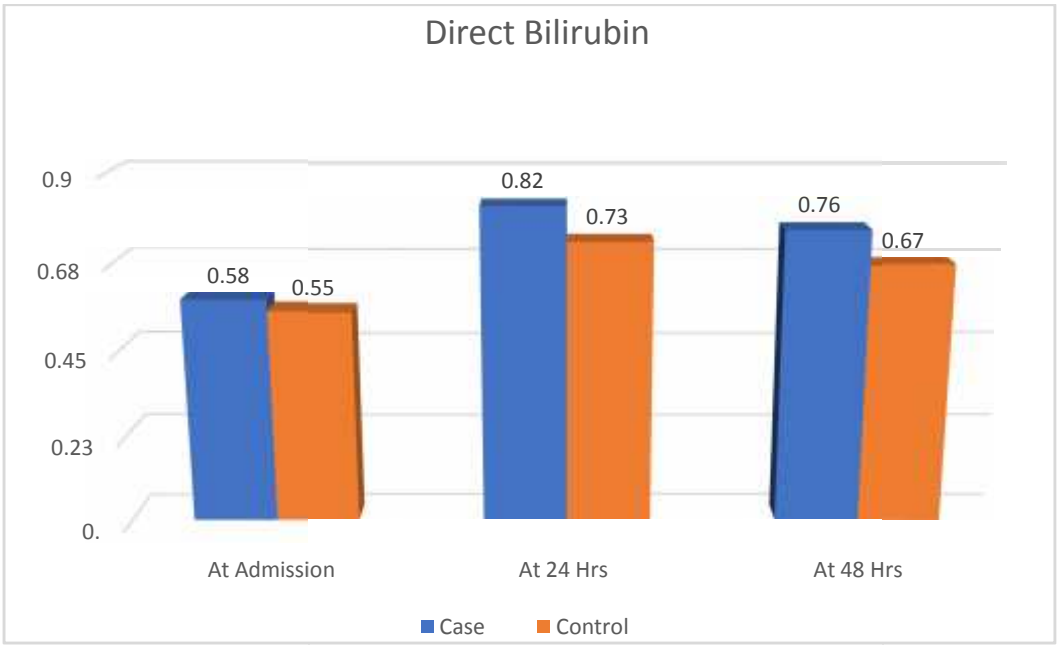


Table 4 : Comparison of Mean Difference of Total Serum Bilirubin between both the group at admission, 24 hours and 48 hours

Mean Difference of Total Serum Bilirubin.	group				P Value
	Case		Control		
	Mean	Standard Deviation	Mean	Standard Deviation	
Between Admission and 24 hours	5.37	2.11	3.61	1.90	0.001
Between Admission and 48 hours	7.36	2.17	6.14	2.35	0.032
Between 24 hours and 48 hours	1.99	2.11	2.53	1.95	0.286

On comparing the mean serum total bilirubin difference the subjects at the time of admission and 24 hour , between admission and 48 hours and between 24 hours and 48 hours was calculated and it was found that between admission and 24 hours 5.37mg/dl , between admission and 48 hours 7.36 and between 24 hours to 48 hours 1.99 mg/dl total serum bilirubin was reduced in the study subjects and it was 3.61 mg/dl , 6.14 mg/dl and 2.53 mg/dl among control groups respectively. The mean difference of serum total serum bilirubin between both the groups was found to be statistically significant between admission and 24 hours and between admission and 48 hours. The P value was found to be statistically insignificant between 24 hours and 48 hours of admission.

Table 5 : Comparison of Mean Difference of Direct Bilirubin between both the group at admission, 24 hours and 48 hours

Mean Difference of Direct Bilirubin.	group				P Value
	Case		Control		
	Mean	Standard Deviation	Mean	Standard Deviation	
Between Admission and 24 hours	-0.26	0.35	-0.13	0.28	0.128
Between Admission and 48 hours	-0.20	0.40	-0.08	0.30	0.162
Between 24 hours and 48 hours	0.06	0.36	0.06	0.30	0.977

On comparing the mean Direct bilirubin difference the subjects at the time of admission and 24 hour , between admission and 48 hours and between 24 hours and 48 hours was calculated and it was found that between admission and 24 hours -0.26mg/dl , between admission and 48 hours -0.20 and between 24 hours to 48 hours 0.06 mg/dl total serum bilirubin was reduced in the study subjects and it was -0.013 mg/dl , -0.08 mg/dl and 0.06 mg/dl among control groups respectively. The mean difference of serum total serum bilirubin between both the groups was found to be statistically insignificant

between admission and 24 hours and between admission and 48 hours and between 24 hours and 48 hours of admission.

Table 6: Distribution of Study subjects based on the Mean Birth weight of the subjects in both the groups

	group				P Value (Independent t test)
	Case		Control		
	Mean	Standard Deviation	Mean	Standard Deviation	
Weight in gms (at admission)	2728.94	429.20	2510.30	398.60	0.036
Weight in gms (at 24hrs)	2734.55	428.79	2506.36	397.00	0.028
Weight in gms (at 48 hrs.)	2736.67	428.00	2509.24	395.79	0.029

The mean weight of the newborn at the time of admission in the study group was found to be 2728.94 $\pm$ 429.20 gms and 2510.30 $\pm$ 398.60 gms in the control group and the association was found to be statistically significant . At 24 hours post admission the mean birth weight in study group was 2734.55$\pm$ 428.79 gms and in control group it was 2506.36$\pm$397.0 gm and the association were found to be statistically significant . At 48

hours the mean birth weight of study subjects in study group was 2736.68±428.0 gms and in control group it was 2509.24± 395.79 gms with significant statistical association between both the groups.

Figure 9 : Graph wise distribution of study subjects based on Birth weight in both the groups

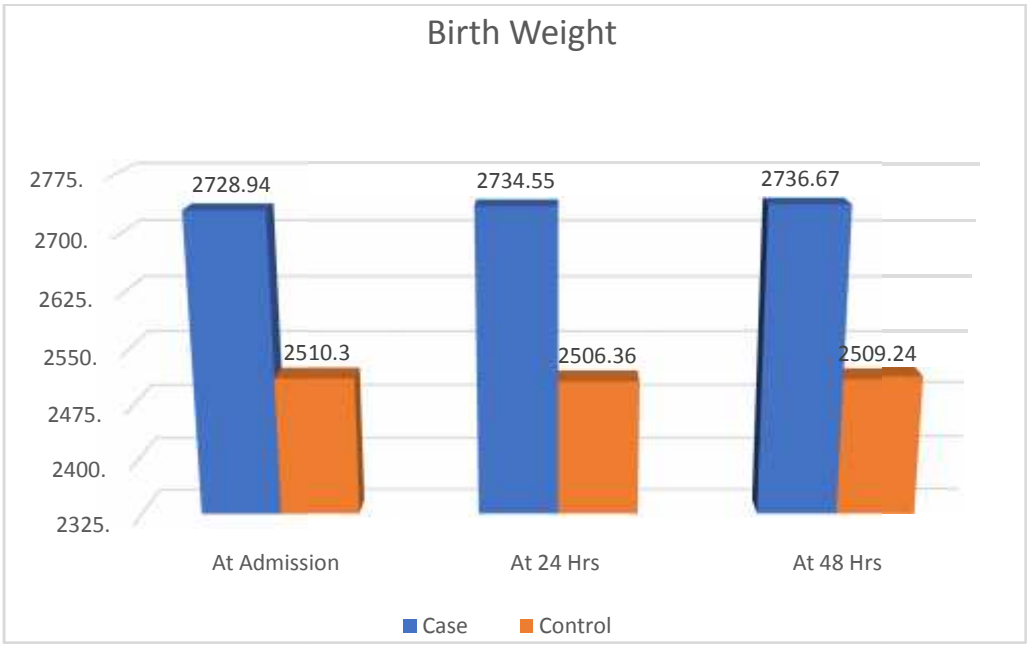


Table 7 : Comparison of Mean Difference of Birth weight between both the group at admission, 24 hours and 48 hours

	group				P Value
	Case		Control		
	Mean	Standard Deviation	Mean	Standard Deviation	
Between Admission and 24 hours	5.61	10.29	-3.94	9.98	0.0001

Between Admission and 48 hours	7.73	14.31	-1.06	16.94	0.026
Between 24 hours and 48 hours	2.12	9.60	-2.88	11.79	0.776

On comparing the Mean Birth weight difference the subjects at the time of admission and 24 hour , between admission and 48 hours and between 24 hours and 48 hours was calculated and it was found that between admission and 24 hours 5.61 gm , between admission and 48 hours -7.73gms and between 24 hours to 48 hours -2.12 gm of birth weight was reduced in the study subjects and it was 3.94 gms , 1..06 gms and -2.288 gms among control groups was seen respectively. The mean Birth weight difference between both the groups was found to be statistically insignificant between admission and 24 hours and between admission and 48 hours and between 24 hours and 48 hours of admission it was found to be statistically insignificant.

Table 8: Distribution of Serum Electrolytes among the study subjects

	Serum Sodium (Mean ±SD)		Serum Potassium (Mean ±SD)		Serum Chlorine	
	At Admission	At 24 hrs	At Admission	At 24hrs	At Admission	At 24 hrs
Cases	143.00±5.58	141.24±3.51	4.94±0.66	4.88±0.60	106.48±6.05	105.42±4.51
Control	142.85±6.20	141.82±5.17	5.12±0.70	5.09±0.68	105.55±5.88	104.94±5.86
P Value	0.917	0.598	0.280	0.183	0.525	0.708

In the present study the mean serum sodium levels at the time of admission in the study group was found to be 143.00±5.58 mmol/L and in the control group group it was 142.85±6.20 with insignificant p value. The Mean Serum Sodium levels at 24 hours was found to be 141.24±3.51 in the study group and 141.85±5.17 mmol/L in the control group with insignificant p value at the level of admission and at 24 hours .

The mean serum Potassium levels at the time of admission in the study group was found to be 4.94±0.66 mmol/L and in the control group group it was 5.12±0.70 with insignificant p value. The Mean Serum Potassium levels at 24 hours was found to be 4.88±0.60 in the study group and 5.09±0.68 mmol/L in the control group with insignificant p value at the level of admission and at 24 hours.

The mean serum Chlorine levels at the time of admission in the study group was found to be 106.48±0.65 mmol/L and in the control group group it was 105.55±5.88 with insignificant p value. The Mean Serum Chlorine levels at 24 hours was found to be 105.42±4.51 in the study group and 104.94±5.86 mmol/L in the control group with insignificant p value at the level of admission and at 24 hours.

Table 9: Distribution of study subjects based on the order of preference by mother for fluid supplementation.

		group			
		Case		Control	
		Count	Column N %	Count	Column N %
What would be the order of preference by mother for fluid supplementation	1	28	84.8%	15	45.5%
	3	5	15.2%	18	54.5%

Chi Square = 11.278 p= 0.001

In the present study nearly 84.8% of the subject's mother preferred ORS Fluid in study group and 15.2% of the mothers preferred Formula feeds in study group. In the control group 45.5% of the mothers preferred ORS and 54.5% of the mothers preferred Formula feeds with a statistical significance p value.

DISCUSSION:

The present randomized control trial was conducted in the department of Pediatrics at JNMC Medical College, Belgaum from June 2020 to May 2021. A total of 66 study subjects were randomized into study and control group based on the study and control by computer generated random number .

The Dr Prabhakar Kore Hospital in the Belgaum which is attached to J N Medical College is a tertiary care center which serves the people in the region and it caters to the health care needs of the community. With Belgaum city being the center for the health needs of the people of three states Karnataka, Goa and Maharashtra it gets most of the high-risk pregnancy and neonates' cases at very late stage of the disease for further treatment. All the new borns in and around the Belgaum will be referred for further treatment of exaggerated Physiological bilirubinemia and for management of Pathological Hyperbilirubinemia.

The most common mode of treatment used in the treatment is Phototherapy and exchange transfusion. But Various studies had shown that fluid supplementation will help in decreasing the total serum bilirubin in the new born rapidly. The extra fluid supplementation will help in decreasing the enterohepatic circulation and it will help in diluting the serum bilirubin and further increases the renal excretion of bilirubin in urine. Further in neonates with significant Hyperbilirubinemia there will be decreased intake of breast milk and insensible water loss during phototherapy that can lead to worsening of hyperbilirubinemia.

This Randomized controlled trial was planned where neonates with hyperbilirubinemia who were in phototherapy range were randomized in two study groups and received 50ml/kg of oral ORS over 16 hours or only standard therapy(Breast feeding phototherapy) to evaluate the efficacy of oral fluid supplementation in neonates with hyperbilirubinemia.

NICU admissions for treatment of phototherapy creates lot of emotional distress among parents because of the separation of baby and mother. Mothers who have difficulty in establishing adequate lactation have guilt feeling for being responsible for exaggeration of jaundice. Early discharge from NICU by giving oral fluids may reduce the duration of phototherapy and thus reassure the parents of baby's wellbeing.

Inadequacy of Breastfeeding prompts the parents to give consent for formula feeds. Use of ORS as fluid in addition to breast feeding discouraged the use of formula feeds in our study group.

Oral fluid supplementation was given to neonates who were assigned to this group at random. The supplement fluid volume was determined based on a fluid deficit of 50 mL/kg (equivalent to mild dehydration). In addition, the newborn was permitted to eat as usual prior to the start of the trial. Oral fluid supplementation was administered through orogastric tube or katori spoon during an 8-hour period, separated into 2-hour intervals. ORS was reconstituted in twofold dilution to match the sodium content in intravenous fluid and had the following composition after dilution: 37.5 mosmol/L sodium, 10 mosmol/L potassium, 32.5 mosmol/L chloride, 5 mosmol/L citrate, 37.5 mosmol/L dextrose, 122.5 mosmol/L total osmolarity

The amount of fluid given varies depending on the study. Iranpour R [2]supplied their research participants with 25% of their daily maintenance and found no advantage, however Mehta et al. found benefit with supplementation of 50% of daily maintenance and found no benefit. Another trial, performed by Goyal P et al,[72] used 50ml/kg and found benefits in lowering blood total bilirubin among the study participants.

Before the start of the study the serum osmolality was calculated and itwas found that in the study group itw as 292.82±12.31 mmol/l and in control group it was 294.09±14.72 mmol/l (normal serum osmolality is between 282mOsm/L to 291mOsm/L) and was also clinical assesed for the degree of malnutrition clinically and further based on the results of the above mentioned studies it was decided to use 50ml/kg as fluid replacement among the study group . We preferred to give fluid supplementation through oral route rather than Intravenous route , because oral route reduce the chances of infection and its painless when compared to intravenous The oral route is also considered safe and easy to administer and also to monitor by the mother .

In the present study the gender distribution was compared and it was found that more than 50% of the study subjects were Female in both the groups and the association was found to be statistically insignificant with p value of 0.805. In the study done by Bandyopadhyay A et al [74] also showed that association between gender and the groups was not statistically significant similar to our study findings. In Another study done by Patil A et al [75] the male to female ratio was more with 1.16:1 which is contrasting to our study findings . The Study done by Goyal P et al [72] also demonstration statistical

insignificant association between gender and the study groups which is comparable and similar to our study findings

Neonates enrolled in study were randomised using computer generated table. However, there is significant difference in mean weight between the study and control group. This is the major limitation of this study. Larger sample size could have helped but because of unprecedented covid pandemic, there was fall in number of admissions and hence there were restrictions in enrolment of neonates in the study. The mean birth weight in our study group was 2921.82+437.30 gms and in control group it was 2706.36+407.19 gms with significant p value of 0.04.

As shown in table no. 2, the maternal blood group is known to play a crucial role in the occurrence of the hyper bilirubinaemia with ABO Incompatibility being one of the major factor contributing for this condition . However, in our study there was no significant association of the Blood Group of the mother and distribution of the neonates in the study and control groups were found to be statistically insignificant with p value of 0.780.

The DCT was found to be positive in only two neonate in which blood group of the mother was B negative and O negative. In the study done by Bandyopadhyay A et al [74]. DCT was negative in nearly 95% of the subjects in study group and 98% in control group with insignificant p value as compared to our study findings .

In the present study the age of admission of the study subjects in the study group was 82.36 hours of life and in control group it was 86.52 hours of life with insignificant p value of 0.608. In the study done by Sarvi M et al [76] the mean age of admission was

5.17 days in study group and 5.07 days in control group with insignificant p value as compared to our study findings . The age at the time of enrollment of the study subjects in the Goyal P et al [72] Study was 83 ±27 hours in study group and 92±33 hours in control group with insignificant p value as comparable to our study findings.

As shown in Table no. 3 and 4 The Mean Serum total bilirubin and Direct Bilirubin was compared between both the group at the time of admission and further compared at 24 hours and 48 hours post admission . On comparing between both the groups serum total bilirubin was found to be reducing in both the groups but the reduction was found to be statistically insignificant . On further analysis it was found that the mean serum total bilirubin was reduced more in the study group when compared to control group. This fall of serum total bilirubin was found to be statistically significant when compared between the level at the time of admission and 24 hours and 48 hours but insignificant when compared between 24 hours and 48 hours .

When Direct bilirubin was evaluated at the level of admission and further at 24 hour and 48 hours there was reduction in count in both groups but the reduction was found to be statistically insignificant at each intervals .

In the study done by Bandyopadhyay A et al [74] and Sarvi M et al [76] demonstrated that the decrease in mean TSB from baseline to study end point among both the study and control groups were evaluated and it was found that TSB levels were decreased in both the groups, but in fluid supplementation group the decreasing percentage was higher and significant similar to our study findings .

In a research conducted by Patil A et al [75], the difference in bilirubin levels and the rate of bilirubin decrease between two groups was not significant.

In a research by Mehta et al.[16], fluid supplementation resulted in a reduction in the rate of exchange transfusion and the duration of phototherapy in term infants with severe hyperbilirubinemia. The case group in this research, on the other hand, was given intravenous hydration for the first 8 hours before being given oral supplementation with expressed breast milk or formula meals.

Boo and Lee [65] found no benefit from oral or intravenous fluid supplementation in extremely jaundiced healthy term newborns undergoing extensive phototherapy in a randomised controlled experiment. However, the amount of fluid provided to both groups (enteral and intravenous) was comparable; the only difference was the manner of delivery (oral vs. intravenous) and the study was limited to the first four hours of phototherapy.

In a research by Goyal P et al.[75], there was no significant difference in the duration of phototherapy or exchange transfusion between non-supplemented and fluid-supplemented neonates undergoing phototherapy for severe hyperbilirubinemia (both intravenous and oral routes). There was a reduction in total blood bilirubin levels when compared to the oral and control groups, however the connection was determined to be statistically insignificant after 8 hours of intervention.

According to the American Academy of Pediatrics [2], there is no evidence that excessive fluid delivery affects serum bilirubin concentrations and that regular intravenous fluid or other supplementation of term and near-term newborns receive phototherapy unless dehydration is present.

Additional fluid supplementation in healthy term infants with unconjugated hyperbilirubinemia decreased the average time of phototherapy by 10.7 hours, according to a Cochrane review of prior trials; however, the therapeutic relevance of this finding remained unclear.[63]

Demirsoy U et al [69] found no significant difference ($p>0.05$) in the mean indirect serum bilirubin level between the two groups at the time of admission to the newborn critical care unit and at 4, 8, 12, 24, and 48 hours following the start of phototherapy and fluids. Between the two groups with and without fluid supplementation, there was no significant difference in the mean duration of phototherapy or the median length of hospitalisation ($p>0.05$).

Saeidi et al. [67] conducted a research in which term infants with severe hyperbilirubinemia were given IV fluid supplementation and showed a considerable decrease in serum bilirubin levels in the first 24 hours, despite no change in the requirement for blood exchange transfusion.

Al-Masri [70] did research to see whether it was required to provide fluid supplements to healthy term newborns during phototherapy. They determined that there was no need to add additional fluid during phototherapy since there was no statistically significant difference in serum bilirubin levels between supplemented and non-supplemented groups at the same time points. The quantity of additional fluid delivered to the supplemented group was only 20% of the maintenance, despite the fact that the fluid utilised was the same as in previous experiments.

Sixty healthy breast-fed newborns with non-hemolytic hyperbilirubinemia were randomly randomised to receive either breast milk only or intravenous fluid in addition to breast milk during conventional phototherapy in a research conducted by Iranpour [66].

Fluidsupplemented neonates got an extra 25% of their daily maintenance fluid needs. They discovered that there was no significant difference between the two groups' mean total blood bilirubin levels at the time of enrolment and 84 hours following phototherapy. This was most likely due to the fact that the IV supplemental fluid they provided was only 25% and was administered over a 24-hour period. This fluid supplementation may not have been enough to treat moderate subclinical dehydration in term newborns with severe non-hemolytic hyperbilirubinemia, which requires at least 50ml/kg over a shorter period of time. We were able to demonstrate a statistically significant decrease in the requirement for blood transfusions and the duration of phototherapy in these newborns using this method.

Enad A S et al [77] conducted another investigation. The rate of bilirubin reduction in the supplemented group was considerably greater than in the non-supplemented group at 4 hours, 8 hours, and 24 hours.

Table no.: 10 Studies done with extra fluid supplementation(IV/Oral) for neonates with Hyperbilirubinemia:

Sl no	Author's	Year	Route of administration	Results(Serum Bilirubin Levels)
1	Bandyopadhyay A et al [74] (n=100)	2017	IV	Reduces the rate of exchange transfusion and the duration of phototherapy by lowering serum bilirubin levels.

2	Sarvi M et al [76] (n=60)	2018	IV	Significant reduction in serum bilirubin levels at 24 and 36 hours, as well as shorter phototherapy time
3	Boo N Y et al [65] (n=54)	2002	IV and oral	The rate of decline in TSB levels during the first 4 hours of vigorous phototherapy was comparable whether they received oral or intravenous fluid replenishment.
4	Demirsoy U et al [69] (n=250)	2011	IV	In healthy term neonates with no dehydration, intravenous fluid supplementation has no influence on the rate of decline in serum bilirubin or the duration of phototherapy.
5	Patil A et al [75] (n=52)	2020	IV	Intravenous fluids had no effect on the rate of serum bilirubin decline following phototherapy in sound, term, breastfeeding infants.

6	Goyal P et al (n=150)[72]	2018	IV and Oral	In the initial few hours of therapy, intravenous fluid augmentation may result in a quicker reduction of STB. However, there was no influence on the total duration of phototherapy or the requirement for exchange transfusions when severe phototherapy was used.
7	Mehta et al [16] (n=74)	2005	IV and Oral	The level of serum total bilirubin was reduced as a consequence of the extra fluid supplementation.
8	Alaa Salman Enad et al [77] (n=52)	2018	IV	In non-hemolytic jaundiced term infants, intravenous additional fluid supplementation might hasten the decline in blood bilirubin levels and shorten the period of phototherapy.

9	Saeidi R et al [67] (n=100)	2009	IV	Supplemental fluids through IV Although there was no change in the requirement for blood exchange transfusion, there was a considerable drop in serum bilirubin levels in the first 24 hours.
10	Al-Masri et al [70] (n=52)	2012	IV	There was no need to add additional fluid during phototherapy since there was no statistically significant difference in serum bilirubin levels between supplemented and non-supplemented groups at the same time points.

Changes in Weight:

The mean weight of the study subjects was estimated regularly at the time of admission, 24 hours and 48 hours and we found that in our study there was no significant weight loss among study subjects in both the group and this difference was also found to be statistically insignificant. The weight gain in study group could be secondary to dehydration because of the extra fluid given in form of ORS. In the another study done by Patil A et al [75] also found no significant weight loss between both the groups in the follow up period also. Similar results was also seen In the study done by Iranpour R et al [66] , Saeidi et al [67]and Boo et al [65] also.

Changes in Electrolytes:

On comparing the serum électrolytes levels and serum osmolarity between both the groups in the present study the sodium levels , Pottasium levels and Serum Cholrine levels were found to be comparable between both the groups and itw as also found that the difference between both the groups was statistically insignificant at the time of admissiona and even after 24 hours post admission. The Findings of serum elecrolytes in our study was comparable to the findings of Goyal P et al[72] and Bandyopadhyay A et al.[74]

As in table no. 9, In the present study nearly 84.8% of the subjects mother preferred ORS Fluid in study group and 15.2% of the mothers preferred Formula feeds in study group. In the control group 45.5% of the mothers preferred ORS And 54.5% of the mothers preferred Formula feeds With a statistical significance p value.

Cocnlusion :

Changes in Bilirubin levels:

By our study we could conclude that there is significant reduction in the Serum total Bilirubin and Direct bilirubin from the time of admission to 24 hours and further at 48 hours . The rate of decrease of the total bilirubin levels was seen rapidly in the initial hours post oral supplementation along with phototherapy but the same effect at 48 hours was found to be insignificant .

Thus we could conclude that fluid supplementation in the neonates with hyperbilirubinemia resulted in faster decline of Serum total bilirubin.

SUMMARY:

- 66 neonates with gestational age more than 34 weeks with hyperbilirubinemia requiring phototherapy were randomized into two groups according to computer generated randomisation chart.

- The study group received ORS solution 50 ml/kg over 16hrs in addition to standard therapy (EBM+Photothertapy). The control group received only standard therapy.

- 48.5% of the newborns were male and 51.5% were female in the study group and 45.5% were male and 54.5/5 were female in the control group (p value 0.805).

- The mean Birth weight of in the study group was 2921.82$\pm$437.0 gms and in the control group it was 2706.36$\pm$ 407.19 gms (p value 0.042).

- In both the groups 9.1% of them were delivered by normal delivery and 90.9% were delivered by cesarean section.

- In the study group 45.5% of mothers had O Positive , 24.2% A Positive,12.1% B Positive, 3% A Negative, 3% B Negative, 6.1% O Negative and 6.1% and AB Negative Blood Groups . Among the control Group A Positive blood group was seen in 27.3%, O positive in 27.3%, B positive in 24.2%, A Negative in 6.1%, O Negative in 6.3%, AB Negative in 6.3% and B Negative in 3% of the mothers.

- The direct Coomb's test was found to be Positive in 6.1% of study group and none in Control group.

- There was no hemolysis on peripheral smear among neonates in the study.

- The Mean age at the time of admission to NICU for the purpose of treatment was found to be 82.36± 29.3 hours in the case group and 86.52±35.78 hours in control group

- At the time of admission the mean total serum bilirubin was 17.18± 3.20 mg/dl in study group and 15.91± 2.70 in control group.

- 24 hours post admission the mean total serum bilirubin level was 11.91± 3.61 mg/dl in study group and 12..27± 2.58 mg/dl , 48 hours the mean total serum bilirubin was 9.76± 2.49 mg/dl in study group and 9.73± 2.23 mg/dl in control group .

- The mean rate of fall in TSB was 5.37mg/dl in 24 hours among the study group while it was 3.61mg/dl in 24hrs in the control group. This difference was statistically significant (p value 0.001)

- Further, the rate of fall in TSB between 24hrs and 48hrs of admission among study group was 1.99mg/dl and in control group it was 2.53mg/dl (p value 0.286)

- There was no statistically difference in fall of TSB after 48hrs in both the groups.

- At 24 hours post admission the mean weight in study group was 2734.55± 428.79 gms and in control group it was 2506.36±397.0 gm.

- Among the study group there was mean weight gain of 5.61 +_10.29 gms between admission and 24 hours while it was 7.73gms+_ 14.31 between admission and 48 hours. In the control group there was weight loss of 3.94 +_9.98 gms , 1.06+_16.94 gms during the same period. This difference was statistically significant at each time period.

- The serum osmolality in the study group was 292.82±12.31 mmol/l and in control group 294.09±14.72 mmol/l . This was at the higher limit of normal range given for neonates in this age group (282mOsm/L - 291mOsm/L)

- In the present study nearly 84.8% of the mothers from study group preferred ORS Fluid and 15.2% of the mothers preferred Formula feeds. In the control group 45.5% of the mothers preferred ORS and 54.5% of the mothers preferred Formula feeds.

Significance and Limitations of the study:

Inadequate oral feeds, high environmental temperatures and poor maternal understanding regarding frequent and exclusive breastfeeding are some of the factors which are known to cause dehydration in neonates leading to exaggeration of physiological jaundice.

In this study we have studied the role of oral ORS to provide extra fluid for healthy neonates in addition to exclusive breast feeding. Thus, augmenting the rate of fall of TSB in the first 48hrs which has been found to be safe and easily implementable. This intervention could be useful in the Level 2 NICUs in the periphery to decrease the duration of NICU stay and prevention of infections secondary to IV fluids. It would

also help in prevention of formula feeding in presence of inadequate breast feeding. However, our sample size was small and was also affected by the covid pandemic. Similar study with a larger sample size in the peripheral level 2 NICU/SNCUs are required to supplement the findings of our study

COCNLUSION

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By our study we could conclude that there is significant reduction in the Serum total Bilirubin and Direct bilirubin from the time of admission to 24 hours and further at 48 hours. The rate of decrease of the total bilirubin levels was seen rapidly in the initial hours post oral supplementation along with phototherapy but the same effect at 48 hours was found to be insignificant.

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ANNEXURE I – CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH

"FLUID ADMINISTRATION IN NEONATES WITH HYPERBILIRUBINEMIA- RCT"

Principal Investigator : **Dr. HIMANSHU ANAND, PG Student**

Co – Investigator: **Dr. MANISHA BHANDANKAR**

You have been asked to involve your child in above said research to be conducted at NICU DrPrabhakarkore hospital & MRC, Belgaum by Dr. HimanshuAnand, PG student in theDepartment of Paediatrics at Jawaharlal Nehru Medical College, Belgaum.

Introduction

PURPOSE OF THE STUDY:

Neonatal jaundice is a common problem treated with adequate feeding and phototherapymay affect the brain function at very hig level if not treated in time.Some babies may havedehydration due toinadequate breast feeding can lead to an increased and exaggeration ofjaundice (Bilirubin levels)leading to longer duration of phototherapy.Phototherapy iscurrently the mainstay of treatment for neonatal hyperbilirubinaemia. Among the supportivemeasures to compliment the effects of phototherapy, fluid supplementation has beenproposed to reduce serum bilirubin levels.In this study we will give extra oral fluis(ORSSolution) to some babies along with breast feeding for 16 hours and monitor the decrease in

levels of bilirubin. There will not be any change in management in bothe the groups.Somebabies will continue on only breast feeding as per the advice from doctor.We will be sendingblood sample of your baby at admissio,24hrs and 48 hours to monitor for bilirubin.

Voluntary participation

Your child's participation in this study is your voluntary decision, whether or not toparticipate will not affect your current or future relationship with KLEs Dr. PrabhakarKoreHospital & MRC, Belgaum.

Risk and benefits

There are no risks involved.

Privacy and Confidentiality

The only people who will know that you are a research participant are member of theresearch team. No information about you or provided by you, during research will bedisclosed to others without your written consent. When the results of the research arepublished or discussed in the conferences, no information will be disclosed that would revealyour identity. Any information obtained in connections with this study and that can beidentified with you remain confidential and will be disclosed only with your permission.

Queries

If you have any queries you may contact**Dr. Himanshu Anand**, Post Graduate StudentDepartment of Pediatrics JNMC,Belagavi-590010Phone No. 99172-00055.

Dr. Manisha Bhandankar Professor, Department of Pediatrics JNMC,Belagavi-590010Phone No.-91642-05166**Dr. Roopa Bellad**ProfessorDepartment Of Paediatrics,K.L.E University'sJawaharlal Nehru Medical College,Belgaum-590010

You will be given a copy of this form for your information and to keep for your records.

STATEMENT OF CONSENT

I hereby voluntarily agree for my participation in this study. I understand that even if I havethe liberty to withdraw at any time. My signature below indicates that I have read or havebeen told about this entire consent form including the risks and benefits and have had all myquestions answered. I will be given a copy of this consent form.

Signature of the authorized representative/ parent: _____

Date: _____

Name: _____

Relation to the Subject: _____

Signature of the witness: _____

Date: _____

Name: _____

Signature of investigator: _____

Date: _____

Name: _____

ANNEXURE II – PROFORMA

INFORMATION OF CHILD:

Name:

Age

Sex: M/F

Birth weight:

Mode of delivery:

Gestational Age:

DOB:

DOA to NICU

DOD:

Address:

Phone No:

Mother's Details:

Mother's Blood Group-

Baby's Blood Group

DCT-

Peripheral Smear-

Hemolysis (Y/N)

TIME	At Admission	24 Hours	48 Hours
TSB			
WEIGHT			
ELECTROLYTES			
BLOOD GROUP			
DCT			
PERIPHERALSMEAR			
SERUM OSMOLARITY			
RENAL FUNCTION TEST			
URINE OUTPUT (no. of times/24hrs.)			

Question to Mother:

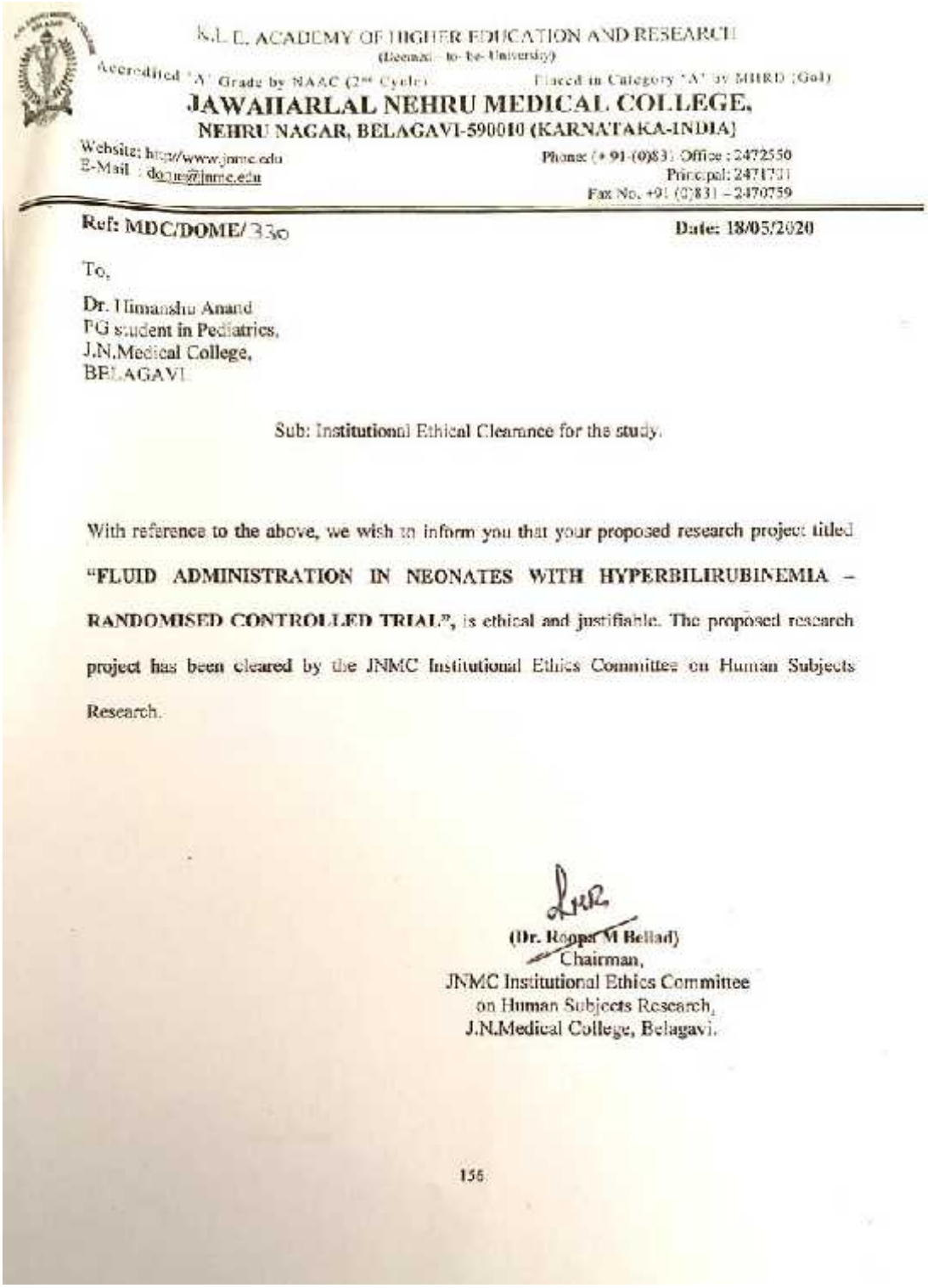
Q.) What would be the order of preference by the mother for fluid supplementationa.)

a) ORS

b) Fluids

c) Formula feeds

ANNEXURE III– ETHICAL CLEARANCE LETTER



K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed - to-be-University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)

JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)

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Principal: 2471731
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/330 **Date: 18/05/2020**

To,

Dr. Himanshu Anand
PG student in Pediatrics,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"FLUID ADMINISTRATION IN NEONATES WITH HYPERBILIRUBINEMIA – RANDOMISED CONTROLLED TRIAL"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

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ANNEXURE IV MASTER CHART

ID	Patient Name (B/O)	Group	DOB	Modeof delivery	GA	Age(hrs)	SEX	Birth weight (gms)	Mother's Blood group	DCT	Hemolysis	TSB (at admission)		TSB (at 24hrs)		TSB (at 48 hrs)		Weight in gms (at admission)	Weight (at 24hrs)	Weight (at 48 hrs)	Electrolytes (at admission)			Electrolytes (at 24hrs)			Serum Osmolarity	Serum Osmo (24hrs)	RFT		Extra fluid (except ORS)	What would be trhe order of preference by mother for fluid supplememtation
												TB	DB	TB	DB	TB	DB				Na	K	Cl	Na	K	Cl			Urea	Creatinine		
1	Kumudini	Case	16-5-20	2	38w+4d	76	2	3100	5	1	1	19.61	0.75	18.57	1.05	10.04	0.45	2880	2880	2890	146	5.95	104	138	5.1	102	305		58	1.01	ORS	1
2	Lalita	Case	16-05-20	2	259	99	2	3300	5	1	1	18.45	0.53	15.09	0.7	12.34	0.84	3080	3080	3090	151	5.97	114	140	6.03	105	308		56	0.9	ORS	1
3	Veena	Control	26-05-20	2	35w+6d	97	2	**2300**	3	1	1	15.52	0.56	6.86	0.68	9.03	0.55	2090	2080	2110	147	4.8	106	154	5.64	116	303	319	39	0.67	No	1
4	Akshata	Case	31-5-20	1	37w+6d	137	1	3500	3	1	1	17.62	0.64	13.57	0.68	10.91	0.48	3400	3400	3410	137	4.56	97	139	5.64	104	282	289	12	0.33	ORS	1
5	Vidyashree	Control	10-06-20	2	35w+1d	169	1	2860	1	1	1	23.5	0.73	16.69	1.06	11.58	1.2	2490	2490	2500	139	4.85	94	135	4.34	100	284	277	22	0.46	No	3
6	Anuradha	Control	16-06-20	2	38w+5d	97	1	2950	3	1	1	19.86	0.68	11.67	0.94	8.96	1.02	2590	2580	2580	145	4.85	107	143	4.39	105	298	295	44	0.45	No	1
7	Vidya	Control	23-06-20	2	37w+6d	*78*	1	3400	7	1	1	17.07	0.51	14.36	0.72	12.97	0.25	3060	3060	3080	146	5.99	106	137	6.31	104	355	316	24	0.47	120ml (L)	3
8	Premlatha T1	Control	25-06-20	2	34w+3d	75	2	1880	1	1	1	13.06	0.36	11.08	0.82	8.5	0.6	1840	1820	1800	144	6.04	106	143	7.01	102	296	294	33	0.73	No	1
9	Anjumlata	Control	30-06-20	2	37w+1d	79	2	2400	1	1	1	16.71	0.54	10.6	1.05	10.73	0.5	2150	2160	2160	148	5.9	109	144	4.37	104	302	294	17	0.66	80ml(L)	1
10	Pratibha T1	Control	27-06-20	2	34w+1d	220	2	2000	6	1	1	14.94	0.34	10	0.46	8.01	0.76	1850	1850	1860	140	5.37	100	138	5.48	97	285	279	22	0.45	No	3
11	Bhagyashree	Control	07-07-20	2	34w+6d	71	1	2700	4	1	1	13.62	0.41	9.4	0.36	7.89	0.32	2420	2420	2430	132	5.75	105	138	5.32	100	270	282	18	0.59	No	1
12	Priyanka	Control	09-07-20	2	36w+6d	57	2	2480	3	1	1	14.36	0.61	12.11	0.84	7.34	0.4	2370	2370	2370	151	4.1	111	144	4.2	108	295	297	26	0.63	No	3
13	Swati	Control	22-07-20	2	39w+4d	72	1	3400	2	1	1	15.76	0.77	13.61	0.77	10.23	0.65	2900	2900	2910	155	5.23	114	152	4.79	115	299	298	46	1.02	No	3
14	Swati	Control	22-07-20	2	34w+6d	108	2	2030	1	1	1	11.51	0.44	7.61	1.03	10.33	0.58	1650	1660	1670	150	4.98	124	151	4.96	120	312	308	62	0.77	120ml(PN)	3
15	Nikita	Case	25-07-20	2	252	179	1	3000	3	1	1	27	1.09	20.26	1.69	16.9	2.35	2720	2720	2730	140	5.16	102	143	4.29	106	286	290	20	0.38	ORS	1
16	Mahadevi	Case	06-10-20	2	40w+4d	79	2	2950	5	1	1	18.13	0.6	12.67	0.68	8.36	0.54	2680	2690	2690	143	3.96	102	139	4.54	103	290	284	13	0.44	ORS	1
17	Tanuja	Control	01-10-20	2	39w+4d	77	2	3000	7	1	1	19.18	0.41	16.62	0.53	13.2	0.72	2990	2990	2980	141	5.66	99	138	4.9	93	282	286	11	0.69	No	1
18	Mandatai	Control	05-10-20	2	39w+1d	84	1	2950	5	1	1	17.7	0.54	12.4	0.62	9.78	0.44	2660	2660	2650	141	5.53	99	140	4.87	101	287	291	13	0.19	No	1
19	Bibi Ayesha	Case	05-10-20	1	38w+4d	92	1	2000	5	1	1	16.87	0.42	8.27	0.25	8.37	0.47	1850	1860	1870	138	5.14	104	138	6.1	103	280	281	12	0.42	ORS	1
20	Shridevi	Control	12-10-20	2	38w+4d	73	2	3000	3	1	1	17.36	0.45	14.13	0.77	8.37	0.28	2770	2770	2760	142	4.92	102	139	5.56	105	289	291	14	0.38	No	1
21	Neeta	Control	17-10-20	2	36w+5d	87	2	2360	1	1	1	15.99	0.64	10.24	0.44	6.38	0.44	1880	1900	1910	146	6.16	105	138	5.43	99	304	286	73	0.75	160ml(L)	3
22	Aishwarya	Case	24-10-20	2	273	81	1	3300	1	1	1	19.51	0.48	12.66	0.41	10	0.36	3100	3110	3110	144	5.5	105	139	4.67	103	300	287	42	0.81	ORS	1
23	Sujata	Case	07-11-20	2	39w+3d	73	1	2650	7	1	1	17.04	0.94	10.36	1	7.01	0.63	2360	2380	2390	150	5.08	116	139	4.98	112	313	298	62	0.93	ORS	1
24	Ankita (T1)	Case	10-11-20	2	36w+2d	121	1	3100	5	1	1	17.31	0.85	11.13	1.29	11.63	0.44	2765	2750	2750	140	5.14	108	138	4.92	110	286	282	12	0.51	43ml(L) +ORS	1
25	Nida	Control	21-11-20	2	259	51	2	2940	5	1	1	16.37	0.6	13.43	1.07	10.53	0.4	2520	2520	2540	142	5.43	104	141	4.7	99	291	290	11	0.4	No	3
26	Priyanka	Control	29-11-20	2	36w+4d	*64*	1	2200	1	1	1	15	0.26	13.1	0.32	10.3	0.37	2060	2060	2070	142	4.91	108	139	5.1	106	292	287	30	0.62	No	1
27	Sneha	Control	09-12-20	2	266	78	2	3260	5	1	1	15.31	0.48	13.65	0.66	10.73	0.8	2970	2960	2970	144	5.24	104	143	5.28	104	295	293	21	0.44	No	1
28	Aarti	Case	31-12-20	2	38w+1d	98	1	3000	5	1	1	17.48	0.52	13.7	0.51	11.55	0.4	2730	2730	2750	139	5.73	110	139	4.63	108	283	285	12	0.39	ORS	3
29	Pooja	Case	12-02-21	2	280	83	2	3400	1	1	1	16.5	0.61	11.32	1.21	10.27	1.14	3040	3060	3070	161	4.43	120	145	4.05	109	327	298	24	0.73	120ml(L) +ORS	1

30	Pooja W.	Case	11-02-21	2	34w+2d	102	1	3220	1	1	1	21.27	0.47	13.95	0.98	12.4	0.4	2700	2720	2730	143	4.06	106	142	5.22	108	290	287	10	0.43	ORS	1
31	Bharti	Case	15-02-21	2	35w+3d	119	2	2800	5	1	1	16.61	0.55	11.3	0.86	9.6	0.92	2570	2580	2600	136	5.3	119	132	4.4	110	292		25	0.3	ORS	1
32	Gulbanu	Control	15-02-21	2	38w+1d	144	1	3100	3	1	1	19.11	0.48	17.2	0.61	13.5	0.72	2810	2810	2815	145	5.15	106	137	4.96	102	294	289	18	0.41	No	3
33	Ashwini	Control	06-03-21	2	38w+2d	64	2	2700	1	1	1	16.93	0.44	14.6	0.62	10.8	0.71	2640	2630	2630	139	4.65	107	139	5.05	109	285	284	17	0.45	No	3
34	Vidyashree	Case	16-03-21	2	36w+6d	77	1	2200	4	2	1	15.71	0.67	9.56	0.43	8.31	0.56	1980	1990	1990	136	4.72	106	144	5.08	109	276	295	28	0.43	ORS	1
35	Bibijaan	Control	16-03-21	2	40w+2d	97	1	2800	3	1	1	17.6	0.82	15.1	0.63	12.4	0.91	2680	2670	2680	142	5.2	108	138	4.92	106	292		16	0.51	No	1
36	Deepika	Case	16-03-21	2	37w+5d	80	2	2840	6	1	1	11.78	0.82	8.58	0.91	8.31	0.92	2570	2580	2590	148	4.1	116	142	4.6	112	313	300	26	0.54	ORS	1
37	Geeta	Case	20-03-21	2	36w+6d	108	1	2500	1	1	1	23.8	0.5	17.7	0.4	14.3	0.43	2460	2480	2470	134	3.5	99	139	4.6	113	286		31	0.5	ORS	1
38	sanjoti	Case	01-04-21	2	259	101	2	2700	5	1	1	16.74	0.57	6.8	0.5	7.2	0.36	2370	2380	2380	139	5.22	111	141	4.48	112	285	287	16	0.42	ORS	1
39	Ambika (T1)	Control	01-04-21	2	36w+3d	78	1	2600	1	1	1	10.76	0.18	8.2	0.42	6.52	0.61	2310	2300	2310	141	6.16	105	138	5.24	104	288		15	0.49	No	3
40	Renuka	Control	06-04-21	2	39w+3d	102	1	3300	5	1	1	12.17	0.91	10.18	0.35	8.24	0.4	3210	3200	3210	131	4.9	104	136	5.88	101	280		14	0.3	No	3
41	Priya	Case	11-04-21	2	259	44	1	3120	5	1	1	13.95	0.56	13.5	1.81	13.78	1.33	2930	2930	2920	145	4.61	110	144	4.49	110	296	295	19	0.63	168ml(ebm+c hm)+ORS	1
42	Vijaylaxmi	Control	12-04-21	2	38w+2d	75	1	2300	3	1	1	15.28	0.81	12.21	0.62	7.08	0.26	2160	2160	2170	138	5.65	109	140	5.22	103	283		28	0.55	No	3
43	Manjula	Case	20-04-21	2	40w+3d	78	2	2800	5	1	1	15.4	0.26	9.19	0.8	7.33	1.12	2580	2600	2600	145	5.31	107	141	5.12	104	299		33	0.37	ORS	1
44	Sana	Case	20-04-21	2	266	93	2	2600	3	1	1	15.69	1.4	6.78	0.93	7.42	1.27	2320	2320	2330	150	5.12	111	144	4.28	111	314	305	63	1.48	ORS	1
45	Suvarna	Control	30-04-21	2	259	51	1	2900	5	1	1	18.5	0.5	14.42	0.71	10.6	0.93	2850	2850	2840	137	4.18	99	141	5.04	103	293		16	0.8	no	3
46	Sheetal	case	30-04-21	2	40w+4d	73	1	3480	5	1	1	20.14	0.48	13.67	1.15	10.77	0.63	3240	3240	3260	141	4.63	108	143	5.13	102	288		17	0.46	ORS	1
47	Changuna	Case	03-05-21	2	37w+3d	47	1	2500	1	1	1	12.6	0.4	7.24	0.8	6.5	1.14	2400	2380	2380	143	4.76	102	140	5.14	104	280		22	0.9	ORS	3
48	Mamta	Control	03-05-21	2	40w+3d	52	2	2400	2	1	1	12.4	0.6	10.6	0.72	7.42	0.54	2340	2350	2350	134	4.2	100	136	5.4	104	310		41	0.5	no	3
49	Mayuri	Case	04-05-21	2	37w+4d	74	1	3600	7	1	1	15.17	0.35	9.81	0.72	7.52	0.61	3450	3470	3460	146	4.72	106	142	3.89	99	292		16	0.8	ORS	1
50	Sumitra	Control	08-05-21	1	266	51	2	3000	5	1	1	13.7	0.97	12.45	1.03	9.56	0.89	2910	2900	2880	146	4.17	119	142	6.11	119	289		31	1	no	3
51	Shashikala	Case	13-05-21	2	40w+3d	49	2	2900	5	1	1	11.4	0.38	6.8	0.45	7.3	0.51	2840	2850	2840	146	4.45	110	141	4.32	99	301		46	0.5	ORS	1
52	Kanchana	Control	12-05-21	1	37w+5d	98	2	2500	3	1	1	14.5	0.31	11.5	0.34	8.36	0.96	2420	2400	2400	130	4.1	101	139	6.19	106	283		28	0.7	No	3
53	Nivedita	Case	21-05-21	2	273	69	2	3200	1	1	1	17.8	0.9	15.24	1.17	11.45	0.9	3020	3030	3020	147	4.96	102	145	5.12	98	294		19	0.16	ORS+96ml L	1
54	Shweta	Case	24-05-21	1	39w+3d	49	2	2600	5	1	1	14.77	0.44	6.05	0.45	9.24	0.72	2540	2540	2530	145	4.92	98	147	5.12	103	289		18	0.76	ORS	1
55	Meera	Case	06-06-21	2	273	71	2	2700	6	2	1	15.36	0.28	10.2	0.81	7.42	1.13	2640	2630	2630	143	5.32	104	145	4.96	98	292		19	1.06	ORS	1
56	Neela	Control	06-06-21	2	39w+1d	124	2	3100	5	1	1	18.48	0.25	12.24	1.21	10.06	0.92	3040	3050	3050	149	5.21	104	145	4.92	101	286		17	0.82	ORS	1
57	Shilpa	Case	10-06-21	2	41w+1d	52	1	3300	1	1	1	17.66	0.47	11.74	0.95	9.82	1.06	3260	3260	3250	141	4.97	98	144	5.12	103	295		23	0.85	ORS	3
58	Soumya	Case	11-06-21	2	36w+3d	51	2	3800	3	1	1	13.65	0.34	9.26	0.72	7.88	0.95	3720	3730	3730	142	4.98	105	147	5.1	99	287		18	1.16	ORS	3
59	Megha	Case	12-06-21	2	266	53	2	2260	1	1	1	15.3	0.4	10.79	0.93	8.62	0.75	2220	2230	2230	138	5.5	99	142	4.89	110	285		40	0.57	ORS	1
60	Laxmi	Case	14-06-21	2	39w+1d	42	2	3100	5	1	1	20.37	0.6	14.72	0.75	10.34	0.88	2880	2880	2870	145	4.02	109	147	5.12	104	300		36	0.64	ORS	1
61	Smita	Control	14-06-21	2	37w+5d	92	1	3000	1	1	1	15.96	0.28	13.31	0.16	15.44	0.59	2850	2830	2840	152	4.46	110	149	4.04	106	294		24	0.36	No	1
62	Arati	Control	17-06-21	1	39w+4d	84	1	2500	5	1	1	18.37	0.53	14.91	0.26	11.48	0.57	2450	2430	2430	136	5.21	102	142	4.93	107	278		15	0.38	No	3
63	Sridevi	Case	18-06-21	2	280	75	1	2800	5	1	1	16.88	0.55	13.67	0.42	9.53	0.79	2760	2750	2740	144	4.09	107	138	5.23	104	276		30	0.75	ORS	1
64	Danamma	Case	19-06-21	2	36w+1d	93	2	2100	2	1	1	19.45	0.63	15.72	1.48	11.75	0.59	2000	2010	2010	133	5.67	99	134	6.12	102	274		35	0.49	ORS	3
65	Nihal	Control	24-06-21	2	37w+1d	59	2	2600	6	1	1	15.56	1.02	12.41	0.95	9.23	0.78	2570	2560	2540	147	4.62	107	152	5.16	109	315		29	0.87	No	1
66	Salma	Control	25-06-21	2	266	47	2	2400	5	1	1	13.28	0.95	9.45	1.06	7.33	0.86	2340	2320	2310	152	5.92	99	149	4.79	105	296		32	0.67	No	1

ANNEXURE V – KEY TO MASTER CHART

SEX:

1 - MALE

2 - FEMALE

MODE OF DELIVERY

1 - NORMAL VAGINAL DELIVERY

2 - LSCS

3 - VENTOUSE

BLOOD GROUP

1- A POSITIVE
2- A NEGATIVE
3- B POSITIVE
4- B NEGATIVE
5- O POSITIVE
6- O NEGATIVE
7- AB POSITIVE
8- AB NEGATIVE

DCT

1- NEGATIVE
2- POSITIVE

HEMOLYSIS

1- NO HEMOLYSIS
2- HEMOLYSIS

FEED PREFERENCE

1- ORS

2-IV FLUIDS

3- FORMULA FEEDS